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CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of lailure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate lor management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) ol hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect; monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy—In animal reproduction studies with nadolol, evidence of embryo-and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia. The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg q.d. (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg q.d. (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and in Unimatic® unit-dose packs of 100 tablets. The 40 mg, 80 mg, and 120 mg potencies are also available in bottles of 1000 tablets. (J3-527D)

References: 1. Epstein M, Oster JR: Beta-blockers and the kidney. Min Electrolyte Metab 8:237-254, 1982. 2. Danesh BJZ, et al: Comparison between short-term renal haemodynamic effects of propranolol and nadolol in essential hypertension: a cross-over study. Clin Sci 67:243-248, 1984. 3. Hollenberg NK: Introduction: β-adrenergic blocking agents—the treatment of hypertension and the kidney. Royal Soc of Med Int Congress and Symposium Series 51:1-8, 1982. 4. Frohlich ED, et al: Long-term renal hemodynamic effects of nadolol in patients with essential hypertension. Am Heart J 108:1141-1143, 1984. 5. Alexander JC, et al: Long-term experience with nadolol in treatment of hypertension and angina pectoris. Am Heart J 108:1136-1140, 1984.

SQUIBB

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*For a discussion of CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, and WARNINGS, including avoidance of abrupt withdrawal, please see brief summary of prescribing information on adjacent page.

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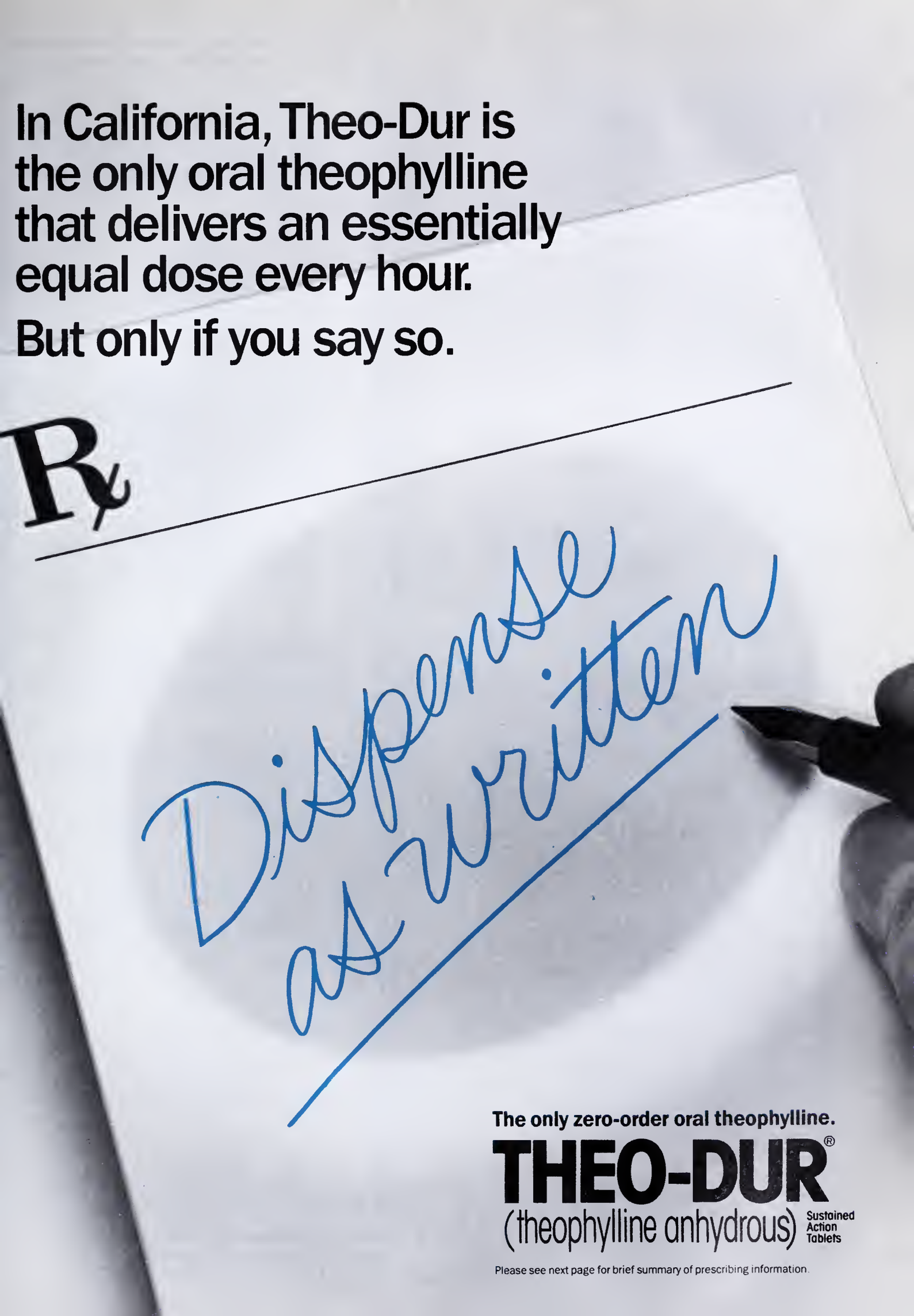

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Indications: THED-DUR is indicated for relief and/or prevention of symptoms of bronchial asthma and for reversible bronchospasm associated with chronic bronchitis and emphysema.

Contraindications: THEO-DUR is contraindicated in individuals who have shown hypersensitivity to theophylline or any of the tablet components.

Warnings: Excessive theophylline doses may be associated with toxicity; serum theophylline levels should be monitored to insure maximum benefit with minimum risk. Incidence of toxicity increases at serum levels greater than 20 mcg/ml. High blood levels of theophylline resulting from conventional doses are correlated with clinical manifestation of toxicity in: patients with lowered body plasma clearances, patients with liver dysfunction or chronic obstructive lung disease, and patients who are older than 55 years of age, particularly males. There are often no early signs of less serious theophylline toxicity such as nausea and restlessness, which may occur in up to 50% of patients prior to onset of convulsions. Ventricular arrhythmias or seizures may be the first signs of toxicity. Many patients who have higher theophylline levels exhibit tachycardia. Theophylline products may worsen pre-existing arrhythmias.

Precautions: THEO-DUR TABLETS SHOULD NOT BE CHEWED OR CRUSHED. Theophylline should not be administered concurrently with other xanthine medications. Use with caution in patients with severe cardiac disease, severe hypoxemia, hypertension, hyperthyroidism, acute myocardial injury, cor pulmonale, congestive heart failure, liver disease, in the elderly (especially males) and in neonates. In particular, great caution should be used in giving theophylline to patients with congestive heart failure. Frequently, such patients have markedly prolonged theophylline serum levels with theophylline persisting in serum for long periods following discontinuation of the drug. Use theophylline cautiously in patients with history of peptic ulcer. Theophylline may occasionally act as a local irritant to the G.I. tract although gastrointestinal symptoms are more commonly centrally mediated and associated with serum drug concentrations over 20 mcg/ml.
Individuals who are rapid metabolizers of theophylline, such as the young, smokers, and some non-smoking adults, may not be suitable candidates for once-daily dosing. These individuals will generally need to be dosed at 12 hourly or sometimes 8 hourly intervals. Such patients may exhibit symptoms of bronchospasm near the end of a dosing interval, or may have wider peak-to-trough differences than desired.

Usage In Pregnancy: Animal reproduction studies have not been conducted with theophylline. It is not known whether theophylline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Xanthines should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It has been reported that theophylline distributes readily into breast milk and may cause adverse effects in the infant. Caution must be used if prescribing xanthines to a mother who is nursing, taking into account the risk-benefit of this therapy.

Pediatric Use: Safety and effectiveness of THEO-DUR administered every 24 hours in children under 12 years of age, and every 12 hours in children under 6 years of age, have not been established.

Adverse Reactions: The most consistent adverse reactions are usually due to overdose and are:

Gastrointestinal: nausea, vomiting, epigastric pain, hematemesis, diarrhea.

Central nervous system: headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.

Cardiovascular: palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, ventricular arrhythmias.

Respiratory: tachypnea.

Renal: albuminuria, increased excretion of renal tubular and red blood cells, potentiation of diuresis.

Others: rash, hyperglycemia and inappropriate ADH syndrome.

How Supplied: THED-DUR 100 mg, 200 mg and 300 mg sustained action tablets are available in bottles of 100, 500, 1000 and 5000, and in unit dose packages of 100.

Caution: Federal law prohibits dispensing without prescription.
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Brochures and registration forms are available from the contact person or organization sponsoring the program.

July 25—**Day of Surgery.** Flagstaff. Friday. Contact: Leonard Wright, MD, (602) 523-4569.

July 26-27—**22nd Annual Coconino County Medical Society Summer Medical Seminar.** Flagstaff. Saturday-Sunday. Contact: Leonard Wright, MD, (602) 523-4569.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6173.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, 44 Gough St, San Francisco 94103; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

September 20—**New Directions in the Treatment of Asthma.** Los Angeles Society of Allergy and Clinical Immunology at Beverly Wilshire Hotel, Beverly Hills. Saturday. Contact: Mrs Geri Coldewey, LASACI, 1626 N Wilcox, #557, Hollywood 90028.

October 7-10—**Rheumatology and Clinical Immunology: A Practical Approach.** UCSF at Stanford Court Hotel, San Francisco. Tuesday-Friday. Contact: UCSF.

October 27-31—**The Western Society of Allergy and Immunology's 25th Annual Session.** Marriott Hotel, Maui, Hawaii. Monday-Friday. Contact: Joyce Gullixson, 1700 SW Columbia, Portland, OR 97201. (503) 224-6159.

December 21-27—**Allergy, Immunology and the Practicing Physician—"Christmas '86—Maui."** Hawaii Medical Association at Royal Lahaina Resort, Kaanapali Beach, Maui. One week. 18 hrs. Fee: $385. Contact: Joe Harrison, MD, Symposium Maui, Inc, PO Box 10185, Lahaina, HI 96761. (808) 879-8182 or 661-8032.

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KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

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★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

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INFORMATION FOR AUTHORS

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In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page. Manuscripts produced with a dot-matrix printer are ordinarily not acceptable.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and the position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

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All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

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If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher, and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

References

References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)" and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

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Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

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This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was oral or written and the person's name, highest academic degree and professional affiliation should be provided.

Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

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Incidence of Most Frequent Adverse Effects as Compared with Placebo in Controlled Clinical Trials

	VASOTEC* n = 2,677	Placebo n = 230
HEADACHE	4.8%	9.1%
DIZZINESS	4.6	4.3
FATIGUE	2.8	2.6
DIARRHEA	1.6	1.7
RASH	1.5	0.4
HYPOTENSION	1.4	0.4
NAUSEA	1.3	1.7
COUGH	1.3	0.9
ORTHOSTATIC EFFECTS	1.3	0.0

*Includes 363 patients treated for congestive heart failure receiving concomitant digoxin and diuretic therapy. Data include adverse effects for VASOTEC with an incidence greater than 1%.

- For the most part, adverse effects were mild and transient and usually did not require discontinuation of therapy.
- In clinical trials, the overall frequency of adverse effects was not related to total daily dosage within the range of 10 to 40 mg.
- Incidence of impotence was only 0.7%.

Angioedema has been reported in patients treated with angiotensin-converting-enzyme inhibitors, including VASOTEC (0.2% of patients treated with VASOTEC). Angioedema associated with laryngeal edema and/or shock may be fatal. **If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately** (see ADVERSE REACTIONS).

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Contraindications: VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product.

Warnings: *Angioedema* Angioedema has been reported in patients treated with angiotensin-converting-enzyme inhibitors, including VASOTEC. Angioedema associated with laryngeal edema and/or shock may be fatal. **If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Neutropenia/Agranulocytosis: Another angiotensin-converting-enzyme inhibitor has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General: Impaired Renal Function:* In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment Dosage reduction of VASOTEC and/or discontinuation of the diuretic may be required

Hyperkalemia Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia (See *Drug Interactions*.)

Surgery/Anesthesia In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, tongue, difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Neutropenia Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC® (Enalapril Maleate, MSD) is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC may attenuate potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril, but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

There are no adequate and well-controlled studies in pregnant women. VASOTEC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2677 patients.

The most frequent clinical adverse experiences in controlled trials were: headache (4.8%), dizziness (4.6%), and fatigue (2.8%). For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences was not related to total daily dosage within the range of 10 to 40 mg. The overall percentage of patients treated with VASOTEC reporting adverse experiences was comparable to placebo.

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.6%), rash (1.5%), hypotension (1.4%), cough (1.3%), nausea (1.3%), and orthostatic effects (1.3%).

Clinical adverse experiences occurring in 0.5% to 1.0% of patients in the controlled trials included.

Cardiovascular: Syncope, orthostatic hypotension, palpitations, chest pain.

Nervous System: Insomnia, nervousness, paresthesia, somnolence.

Gastrointestinal System: Abdominal pain, vomiting, dyspepsia.

Other: Dyspnea, muscle cramps, hyperhydrosis, impotence, pruritus, asthenia.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema and/or shock may be fatal. If angioedema of the face, tongue, or glottis occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately (See WARNINGS.)

Hypotension: Combining the results of clinical trials in patients with hypertension or congestive heart failure, hypotension (including postural hypotension and other orthostatic effects) was reported in 2.3% of patients following the initial dose of enalapril or during extended therapy In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. (See WARNINGS.)

Clinical Laboratory Test Findings:

Hyperkalemia (See PRECAUTIONS.)

Creatinine, Blood Urea Nitrogen. Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.)

Hemoglobin and Hematocrit. Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in hypertensive patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

In overseas marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

For more detailed information, consult your MSD representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

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REFERENCES:
[1]Aasenden R and Peebles T. Effects of fluoride supplementation from birth on human deciduous and permanent teeth. Arch Oral Biol 1974; 19:321.
[2]Hambert L. Controlled trial of fluoride in vitamin drops for prevention of caries in children. Lancet 1971 Feb. 27; p 442.
[3]Newbrun E. How Fluoride Works: Topical vs. Systemic Action, in Mead Johnson Clinical Report Series, Clinical Importance of Fluoride Nutrition in Infants, Children and Young Adults, Chicago, Pragmaton®, 1985, p 7.

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to help you guard appropriate patients against caries risk and nutritional risk.

INDICATIONS AND USAGE: Prophylaxis of vitamin deficiencies and dental caries in children and adults when fluoride of water supply does not exceed 0.7 ppm.[1,2,3] And, in the case of TRI-VI-FLOR® 0.25 mg Drops with Iron and POLY-VI-FLOR® Drops and Chewable Tablets with Iron, prophylaxis against iron deficiencies. Note: VI-FLOR Drops do not contain folic acid because the vitamin is not stable in liquid form.

PRECAUTIONS: Do not exceed recommended dose or give concurrently with other medications containing significant amounts of fluoride. Prolonged excessive fluoride intake may cause dental fluorosis. All VI-FLOR® with Iron products: as with all products containing iron, parents should be warned against excessive dosage. The bottle should be kept out of reach of children.

Keep all VI-FLOR with Iron products tightly closed and away from direct light.

VI-FLOR Drops should be dispensed in the original plastic container, since contact with glass leads to instability and precipitation.

ADVERSE REACTIONS: Allergic rash has rarely been reported.

DOSAGE AND ADMINISTRATION:

Supplemental Fluoride Dosage Schedule (mg/day)*

Age	Concentration of Fluoride in Drinking Water (ppm)		
	<0.3	0.3-0.7	>0.7
2 wk-2 yr**	0.25	0	0
2-3 yr	0.5	0.25	0
3-16 yr	1.0	0.5	0

*From the American Academy of Pediatrics Committee on Nutrition statement, Fluoride Supplementation: Revised Dosage Schedule. Pediatrics 63(1):150-152, 1979.

**The Committee favors initiating fluoride supplementation shortly after birth in breast-fed infants (0.25 mg F/day). In formula-fed infants, fluoride supplementation should be according to the fluoride content of the water used to prepare formula.

PRODUCT	FORM	SIZE	FLUORIDE mg/dose
POLY-VI-FLOR 0.25 mg	Drops	50 ml Bottle	0.25
POLY-VI-FLOR 0.25 mg with Iron	Drops	50 ml Bottle	0.25
POLY-VI-FLOR 0.5 mg	Drops	50 ml Bottle	0.5
POLY-VI-FLOR 0.5 mg with Iron	Drops	50 ml Bottle	0.5
POLY-VI-FLOR 0.5 mg	Tablets	Bottle of 100	0.5
POLY-VI-FLOR 0.5 mg with Iron	Tablets	Bottle of 100	0.5
POLY-VI-FLOR 1.0 mg	Tablets	Bottle of 100	1.0
POLY-VI-FLOR 1.0 mg with Iron	Tablets	Bottle of 100	1.0
TRI-VI-FLOR 0.25 mg	Drops	50 ml Bottle	0.25
TRI-VI-FLOR 0.25 mg with Iron	Drops	50 ml Bottle	0.25
TRI-VI-FLOR 0.5 mg	Drops	50 ml Bottle	0.5
TRI-VI-FLOR 1.0 mg	Tablets	Bottle of 100	1.0

REFERENCES:

1. Hennon DK, Stookey GK and Muhler JC: The Clinical Anticariogenic Effectiveness of Supplementary Fluoride-Vitamin Preparations—Results at the End of Four Years. J Dentistry for Children 34:439-443 (Nov) 1967.
2. Hennon DK, Stookey GK and Muhler JC: The Clinical Anticariogenic Effectiveness of Supplementary Fluoride-Vitamin Preparations—Results at the End of Five and a Half Years. Pharmacology and Therapeutics in Dentistry 1:1-6 (Oct) 1970.
3. Hennon DK, Stookey GK and Muhler JC: Prophylaxis of Dental Caries: Relative Effectiveness of Chewable Fluoride Preparations With and Without Added Vitamins. J Pediatrics 80:1018-1021 (June) 1972.

VI-SOL®/VI-FLOR® products are the nation's most prescribed children's vitamin and fluoride-vitamin supplements.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 13)

ANESTHESIOLOGY

August 17-22—**Clinical Anesthesia.** California Society of Anesthesiologists at The Waiohai Hotel, Poipu Beach, Kauai. Sunday-Friday. 20 hrs. Contact: Linda P. Londerville, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

September 6-7—**Case Conference.** California Society of Anesthesiologists and Travenol Laboratories at High Sierra Hotel, Lake Tahoe. Saturday-Sunday. 9 hrs. Contact: Linda P. Londerville, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

September 26-28—**Anesthesia Practice 1986.** Anesthesiology Educational Foundation at Monterey. Friday-Sunday. 10.5 hrs. Contact: Anesthesiology Educational Foundation, PO Box 24230, Federal Bldg, Los Angeles 90024.

October 22-28—**Post-ASA Annual Meeting.** California Society of Anesthesiologists at Maui Inter-Continental Hotel, Hawaii. Wednesday-Tuesday. 20 hrs. Contact: Linda P. Londerville, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

CANCER

September 25-26—**Advances in Treatment of Leukemia and Marrow Stem Cell Disorders.** UCSF at Sheraton Wharf Hotel, San Francisco. Thursday-Friday. 9 hrs. Fee: $100. Contact: UCSF.

October 27-29—**10th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Island Hotel East, San Diego. Monday-Wednesday. 22 hrs. Fee: $350. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy, San Diego 92121. (619) 453-6222.

CARDIOLOGY

July 25—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Friday. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

July 26-27—**Hemodynamic Monitoring/Pulmonary Artery Catheterization.** STAN. Saturday-Sunday. 15 hrs. Fee: $350. Contact: STAN.

August 1-2—**Coronary Heart Disease and Arrhythmias: Diagnosis and Management.** Creighton University at Sheraton Hotel, Anaheim. Friday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or in Colorado (303) 798-9682.

August 3-7—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Thursday. 18 hrs. Fee: $325. Contact: UCD.

September 10-11—**54th Annual Fall Symposium and 19th Annual George C. Griffith Scientific Lec-**

ture. American Heart Association, Los Angeles, at Hilton Hotel, Los Angeles. Wednesday-Thursday. Contact: Marianne Joyce, AHA, 3550 Wilshire Blvd, Los Angeles 90010. (213) 385-4231.

September 18-20—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Hotel Meridien, San Francisco. Thursday-Saturday. 15 hrs. Fee: $350. Contact: UCSF.

September 22-26—**American College of Chest Physicians 52nd Annual Scientific Assembly.** San Francisco. Monday-Friday. Contact: ACCP, Division of Education, 911 Busse Highway, Park Ridge, IL 60068. (312) 698-2200.

October 10-11—**Vascular and Pulmonary Diseases: Diagnosis and Management.** Medical Education Resources at Sheraton at Fisherman's Wharf, San Francisco. Friday-Saturday. 11 hrs. Fee: $295. Contact: Medical Education Resources, Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or in Colorado (303) 798-9682.

October 16-18—**10th Annual Cardiology Update—1986.** American College of Cardiology at Quail Lodge, Carmel. Thursday-Saturday. Contact: ACC, 9111 Old George Town Rd, Bethesda, MD 20814. (301) 897-5400, ext 227.

October 24-26—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

November 1—**The Heart and the Brain: Clinical Interrelationships—Office Management of Stress and Emotionally Induced Cardiovascular Disabilities.** UCI at Center for Health Education, Long Beach. Saturday. Contact: UCI.

December 12-13—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Americana Canyon Hotel, Palm Springs. Friday-Saturday. 11 hrs. Fee: $295. Contact: Medical Education Resources, Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or in Colorado (303) 798-9682.

December 12-14—**Advances in Heart Disease.** American College of Cardiology at Hyatt Regency on Union Square, San Francisco. Friday-Sunday. Contact: ACC, 9111 Old George Town Rd, Bethesda, MD 20814. (301) 897-5400, ext 227.

DERMATOLOGY

August 20-24—**Advanced Seminars in Dermatology.** UCSF at Hyatt Lake Tahoe. Wednesday-Sunday. Contact: UCSF.

September 21—**1 Day Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Kona Kai Club, San Diego. Sunday. 7 hrs. Fee: $185. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

September 22-28—**Combined Skin Pathology.** UCI at Newporter Inn, Newport Beach. Monday-Sunday. Contact: UCI.

September 28—**1 Day Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Holiday Inn on Union Square, San Francisco. Sunday. 7 hrs. Fee: $185. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

October 3-4—**15th Annual Mycology Review.** Stanford. Friday-Saturday. Contact: Paul H. Jacobs, MD, Dept of Dermatology, Stanford Medical Center, Stanford 94305. (415) 497-6105.

October 11-12—**The Skin From A to Z.** UCSF. Saturday-Sunday. Contact: UCSF.

October 18—**Dermatology.** Kaiser Permanente Medical Group at Ramada Renaissance Hotel, Long Beach. Saturday. 7 hrs. Fee: $100. Contact: Judy Harrison, Dept of Clinical Services, Southern California Permanente Medical Group, 393 E Walnut St, Pasadena 91188. (818) 405-5000.

EMERGENCY MEDICINE

July 16-20—**Update on Trauma.** Mercy Medical Center, Redding at Mt Shasta/Trinity (bicycle tour). Wednesday-Sunday. 10 hrs. Fee: $195. Contact: Shelley Underwood, Inservice Education, PO Box 6009, Redding 96099. (916) 225-6171.

July 18-20—**Update on Trauma.** Mercy Medical Center, Redding at Klamath River (rafting trip). Friday-Sunday. 10 hrs. Fee: $125. Contact: Shelley Underwood, Inservice Education, PO Box 6009, Redding 96099. (916) 225-6171.

July 22-26—**Expedition and Mountain Medicine.** Mercy Medical Center, Redding at Mt Shasta (mountain climbing). Tuesday-Saturday. 10 hrs. Fee: $150. Contact: Shelley Underwood, Inservice Education, PO Box 6009, Redding 96099. (916) 225-6171.

August 8-10—**Wilderness Emergency Care.** Mercy Medical Center, Redding at Klamath River (rafting trip). Friday-Sunday. 10 hrs. Fee: $125. Contact: Shelley Underwood, Inservice Education, PO Box 6009, Redding 96099. (916) 225-6171.

August 9-16—**Updates in Wilderness and Environmental Medicine.** University of Arizona at Otter Bar Lodge, Forks of Salmon (near Eureka). One week. Contact: Epic Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

August 18-22—**Postgraduate Institute for Emer-**

(Continued on Page 26)

PHYSICIANS ADDRESS THE ISSUES AT THE UTAH STATE MEDICAL ASSOCIATION ANNUAL MEETING

September 10, 11, 12, 1986
The Yarrow
Park City, Utah

Schedule of Events

Wednesday, September 10

9:00 AM	**Hospital Medical Staff Section**
9:30 AM	**USMA House of Delegates Opening Session**
12:00 NOON	**Luncheon** *Speaker: John J. Coury, Jr., M.D.* *President-Elect* *American Medical Association*
1:30 PM	**Reference Committee Meetings**
4:00 PM	**USMA House of Delegates**
7:30 PM	**Barbeque**

Thursday, September 1

7:00 PM — ***Fun Run - 3k and 10k Races***

9:00 AM — ***Converging Pressures: A Changing Profession***
Forum on Medical Issues

Entrepreneurialism and Professionalism: When Do They Conflict?
George D. Lundberg, M.D., Editor,
Journal of American Medical Association

A Federal Solution to the Malpractice Crisis
David N. Sundwall, M.D., Staff Assistant
Labor & Human Resources Committee, U.S. Senate

Making Decisions Washington Style: The Doctor's Dilemma
John C. Nelson, M.D., Commissioner
Federal Prospective Payment Assessment Commission

Physician Alternatives in Health Care Delivery
Allan H. Goodman, M.D., Chairman of the Board
Western Health Plans, Inc.,
San Diego California.

12 Noon — ***Luncheon Speaker: Ambassador David Kennedy***

Afternoon — ***Golf - Tennis***

6:30 PM — ***Presidents' Dinner***

Friday, September 12

9:00 AM — ***Medical Problems with Social Consequences***

Aids
Paul A. Volberding, M.D.
Chief, AIDS Activities Division
San Francisco General Hospital

Alzheimers
Murray Raskin, M.D.
Director for Geriatric Research, Education And Clinical Center
Seattle & American Lake VA Hospitals
(Speaker sponsored by Roerig-Pfizer Company)

Abuse of Children
Frederic N. Silverman, M.D.
Clinical Professor of Radiology
University of California, San Francisco

12:00 Noon — ***Luncheon Meeting***

Medical Liability Loss Prevention
Special training for Prevention Coordinators & practical information for doctors who wish to minimize risk of malpractice in their hospitals and offices.
John B. Stanchfield, M.D.
Medical Director
Utah Medical Insurance Association

Reservation forms available from:
USMA, 540 East Fifth South, Salt Lake City, UT 84102 • (801) 355-7477

(Continued from Page 23)

gency and Primary Care Physicians. UCSD. Monday-Friday. Contact: UCSD.

August 25-29—**Topics in Emergency Medicine.** UCSF at Union Square Holiday Inn, San Francisco. Monday-Friday. 32.5 hrs. Fee: $400. Contact UCSF.

August 26-29—**Update in Emergency Medicine.** Mercy Medical Center, Redding at Marble Mountain Wilderness (horse-packing). Tuesday-Friday. 10 hrs. Fee: $195. Contact: Shelley Underwood, Inservice Education, PO Box 6009, Redding 96099. (916) 225-6171.

August 30-September 1—**Wilderness Emergency Care.** Mercy Medical Center, Redding at Klamath River (rafting trip). Saturday-Monday. 10 hrs. Fee: $125. Contact: Shelley Underwood, Inservice Education, PO Box 6009, Redding 96099. (916) 225-6171.

September 22-26—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD at Vacation Village Resort, San Diego. Monday-Friday. Contact: UCSD.

October 27-31—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD at Hanalei Hotel, San Diego. Monday-Friday. Contact: UCSD.

December 7-13—**Current Concepts in Emergency Care.** American College of Emergency Physicians at Royal Lahaina Resort, Maui. Sunday-Saturday. 25 hrs. Contact: Georgine Elich, Kailani World Travel, 4192 Meridian Ave, Bellingham, WA 98226. USA (800) 426-2561 or in Washington (800) 562-2597.

December 8-12—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD. Monday-Friday. 32 hrs. Fee: $325-440. Contact: UCSD.

INTERNAL MEDICINE

July 21-25—**Internal Review of Internal Medicine.** USC at Los Angeles. Monday-Friday. Contact: UCSD.

August 17-22—**New Advances in Internal Medicine.** UCD at Hyatt Regency, Monterey. Sunday-Friday. Contact: UCD.

August 25-30—**7th Comprehensive Nephrology Review.** UCLA at Miramar Sheraton, Santa Monica. Monday-Saturday. 55.5 hrs. Fee: $695. Contact: UCLA.

September 19-20—**Internal Medicine.** Kaiser Permanente Medical Group at Disneyland Hotel, Anaheim. Friday-Saturday. 11 hrs. Fee: $150. Contact: Judy Harrison, Dept of Clinical Services, Southern California Permanente Medical Group, Pasadena 91188. (818) 405-5000.

OB/GYN

July 17-18—**14th Annual Seminar on Breastfeeding for Physicians.** La Leche League International at Hotel Del Coronado, San Diego. Thursday-Friday. 15 hrs. Contact: Carol Kolar, 9616 Minneapolis, PO Box 1209, Franklin Park, IL 60131-8209.

July 24-27—**E.J. Quilligan Conference on OB/GYN.** UCI at Hotel Del Coronado, San Diego. Thursday-Sunday. 14.5 hrs. Contact: UCI.

August 6-9—**Techno-Gynecology 1986.** UCI at Irvine Hilton and Towers. Wednesday-Saturday. Contact: UCI.

August 9-15—**Current Trends in Reproductive Endocrinology, Infertility and Contraception.** USC at Waimea Beach Hotel, Maui. Saturday-Friday. 21.5 hrs. Fee: $525. Contact: USC.

August 14-16—**Advanced Colposcopy.** American College of Obstetricians and Gynecologists at Fairmont Hotel, San Francisco. Thursday-Saturday. 16 hrs. Contact: ACOG, 600 Maryland Ave SW, Ste 300E, Washington, DC 20024-2585.

October 2-5—**Advance Fetal Heart Monitoring.** UCI at Napa Valley. Thursday-Sunday. Contact: UCI.

October 10-11—**OB/GYN Ultrasound and Sonography—Update.** Sacramento Radiology Research and Education Foundation and Northern California Radiology Society. Friday-Saturday. 10 hrs. Fee: $125. Contact: John P. McGahan, MD, Sacramento Radiology Research and Education Foundation, PO Box 19184, Sacramento 95819.

October 20-24—**16th Annual Review Course in Obstetrics and Gynecology.** USC at Pasadena Hilton Hotel. Monday-Friday. 38 hrs. Fee: $545. Contact: USC.

October 20-25—**9th Annual Review Course in Clinical Obstetrics and Gynecology and/or Gynecological Histopathology.** UCI at Westin South Coast Plaza, Costa Mesa. Monday-Saturday. 17-46.5 hrs. Contact: UCI.

October 25—**Review Course for Gynecologic Pathology.** USC at Pasadena Hilton Hotel. Saturday. 6 hrs. Fee: $105. Contact: USC.

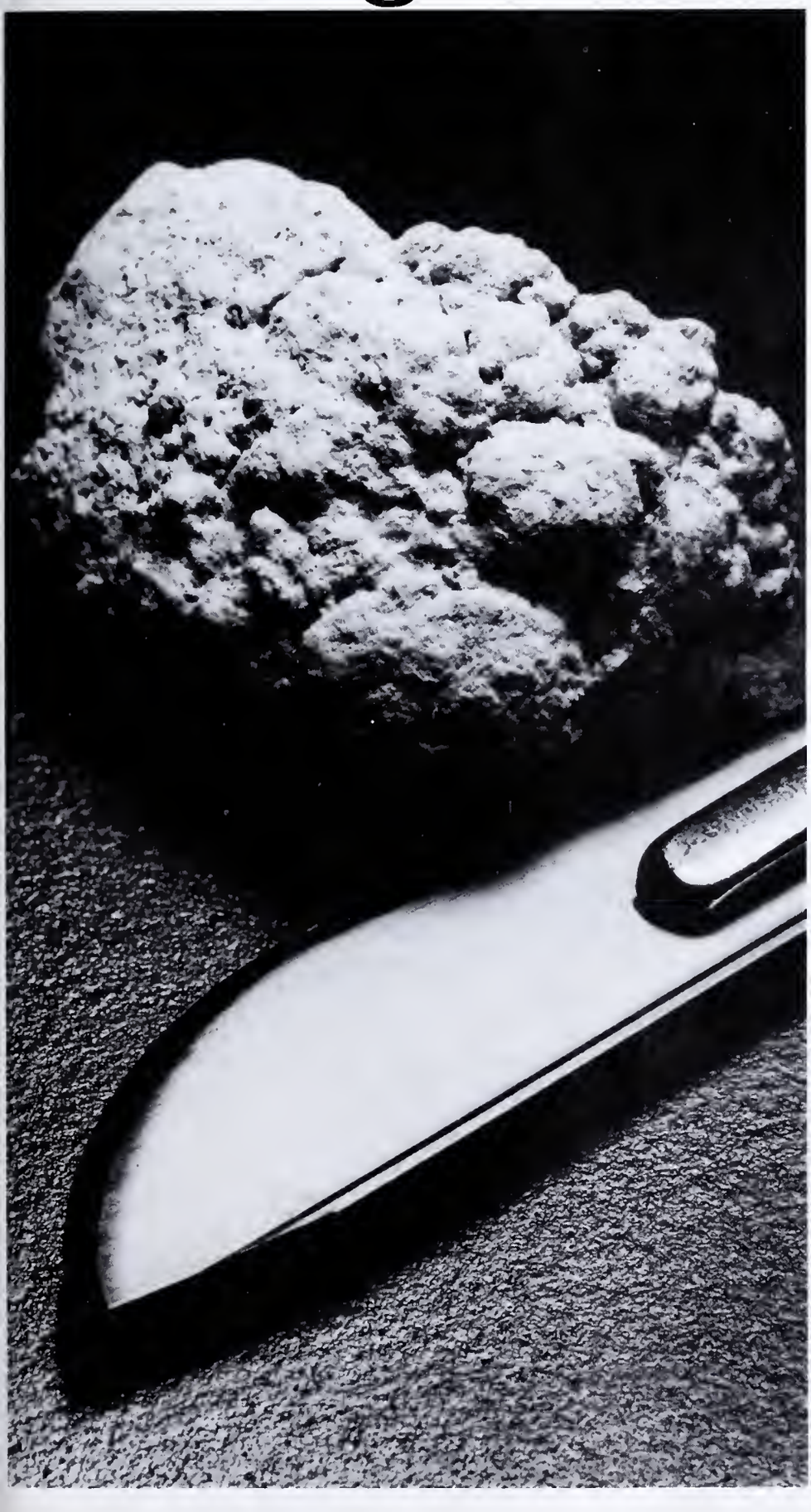
October 29—**Breast Disease Symposium.** UCSF at US Grant Hotel, San Diego. Wednesday. Contact: R. Dawne Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

December 4-7—**Current Issues in Perinatal Medicine.** UCI at Desert Princess Hotel, Palm Springs. Thursday-Sunday. Contact: UCI.

December 11-13—**Advanced Ultrasound.** American College of OB/GYN at Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. 16 hrs. Contact: ACOG, 600 Maryland Ave SW, Ste 300 East, Washington, DC 20024-2588. (202) 863-2542.

(Continued on Page 28)

We're bringing urologists out of the Stone Age.



Now you can give your patients an inexpensive, timesaving alternative to invasive kidney stone surgery: Extra Corporeal Shock Wave Lithotripsy at the Western Kidney Stone Center.

Our open staff privileges allow trained, qualified urologists quick and easy access to an FDA approved Dornier lithotripter. Revolutionary, non-invasive technology that can not only crumble a kidney stone, but also split the cost of conventional surgery in half for your patient. It also has the ability to change weeks of recovery into days.

If you haven't yet received lithotripsy training, our program can assist you in getting the specialized education needed to perform the procedure. In the meantime, we can refer you to a trained urologist who will work with you, not in place of you. One who will supply you with a complete description of your patients' case, operative notes, and specific follow-up care needs. All patients are sent back to the referring physician for follow-up care.

Bottom Line: The Western Kidney Stone Center gives urologists the ability to recommend lithotripsy, without recommending another doctor. It's a service that will not only help you keep your patients, but one that will also keep you in the forefront of your profession.

Call our Clinical Coordinator for more information on the procedure, eligibility criteria, and scheduling dates.

If you're out-of-state, dial: 1-800-84STONE.

If you're in-state: 1-800-64STONE.

Western Kidney Stone Center

At Community Hospital of Los Gatos
815 Pollard Road
Los Gatos, CA 95030

A NATIONAL MEDICAL ENTERPRISES FACILITY

(Continued from Page 26)

OPHTHALMOLOGY

December 11-12—**An Update in Neuro-Ophthalmology.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Friday. Contact: UCSF.

PATHOLOGY

October 20-25—**9th Annual Review Course in Clinical Obstetrics and Gynecology and/or Gynecological Histopathology.** UCI at Westin South Coast Plaza, Costa Mesa. Monday-Saturday. Contact: UCI.

October 25—**Review Course for Gynecologic Pathology.** USC at Pasadena Hilton Hotel. Saturday. 6 hrs. Fee: $105. Contact: USC.

November 12-14—**International Symposium on Medical Virology.** UCI at Disneyland Hotel, Anaheim. Wednesday-Friday. 20 hrs. Fee: $200-225. Contact: Dr Luis M. de la Maza, Dept of Pathology, Rte 84, UCI, 101 City Dr South, Orange 92668. (714) 634-6868.

PEDIATRICS

July 19-27—**4th National Kaiser Permanente Pediatrics Conference.** Oakland Kaiser Hospital at Sheraton Royal Waikoloa Hotel, Hawaii. Saturday-Sunday. 22.5 hrs. Contact: The Permanente Medical Group, 280 W MacArthur Blvd, Oakland 94611. (415) 428-5000.

August 13-16—**Pediatric Respiratory Disease Update: A California Perspective.** Sutter Community Hospital at Wailea, Maui. Wednesday-Saturday. 12 hrs. Fee: $150. Contact: Betsy Stone, Sutter Community Hospitals, 52nd and F Streets, Sacramento 95819.

September 3-5—**Pediatric Trauma 1986: The Practice and Controversies.** San Diego Children's Hospital at Hotel Inter-Continental, San Diego. Wednesday-Friday. Fee: $400. Contact: Unconventional, Inc, PO Box 33185, San Diego 92103. (619) 692-9115.

September 24-25—**43rd Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at the Hilton Hotel, Los Angeles. Wednesday-Thursday. Contact: Eve Black, PO Box 2022, Inglewood 90305. (213) 757-1198.

October 16-18—**Practical Topics in Pediatric Nutrition.** UCSF. Thursday-Saturday. 15 hrs. Fee: $250. Contact: UCSF.

October 17-19—**Current Advances in Pediatrics: 3rd Annual American Academy of Pediatrics Disneyland Seminar.** AAP, Orange County Pediatric Society and UCI at Anaheim. Friday-Sunday. Contact: California Chapter 4, AAP, PO Box 1297, Orange 92668.

October 24-25—**Pediatric Symposium.** Kaiser Permanente Medical Group at Biltmore Hotel, Los Angeles. Friday-Saturday. 12 hrs. Fee: $150. Contact: Judy Harrison, Dept of Clinical Services, Southern California Permanente Medical Group, 393 E Walnut St, Pasadena 91188. (818) 405-5000.

October 25-November 1—**Pediatrics for the Practitioner.** UCI at Mauna Kea Hotel, Hawaii. One Week. Contact: UCI.

November 13-15—**New Approaches in Children's Orthopaedics.** UCD at Monterey Plaza, Monterey. Thursday-Saturday. 9 hrs. Fee: $340. Contact: UCD.

November 21-24—**American Academy of Pediatrics Las Vegas Seminars.** Caesars Palace, Las Vegas. Friday-Monday. Contact: AAP, (213) 757-1198.

PSYCHIATRY

December 28-January 3—**Psychiatry and the Practicing Physician—"New Year '87—Maui."** Hawaii Medical Association at Royal Lahaina Resort, Kaanapali Beach, Maui. Sunday-Saturday. 16.5 hrs. Fee: $385. Contact: Joe Harrison, MD, Symposium Maui, Inc, PO Box 10185, Lahaina, HI 96761. (808) 879-8182.

RADIOLOGY

August 5-8—**Interventional Radiology.** UCSF at San Francisco Hyatt Regency. Tuesday-Friday. Contact: UCSF.

August 25-28—**Annual Napa Valley Radiology Conference.** Sacramento Radiology Research and Education Foundation and the Northern California Radiology Society at Silverado Inn, Napa. Monday-Thursday. 20 hrs. Fee: $360. Contact: John P. McGahn, MD, Sacramento Radiology Research and Education Foundation, PO Box 19184, Sacramento 95819.

August 25-29—**Radiology.** USC at Kaui, Hawaii. Monday-Friday. 27 hrs. Fee: $535. Contact: USC.

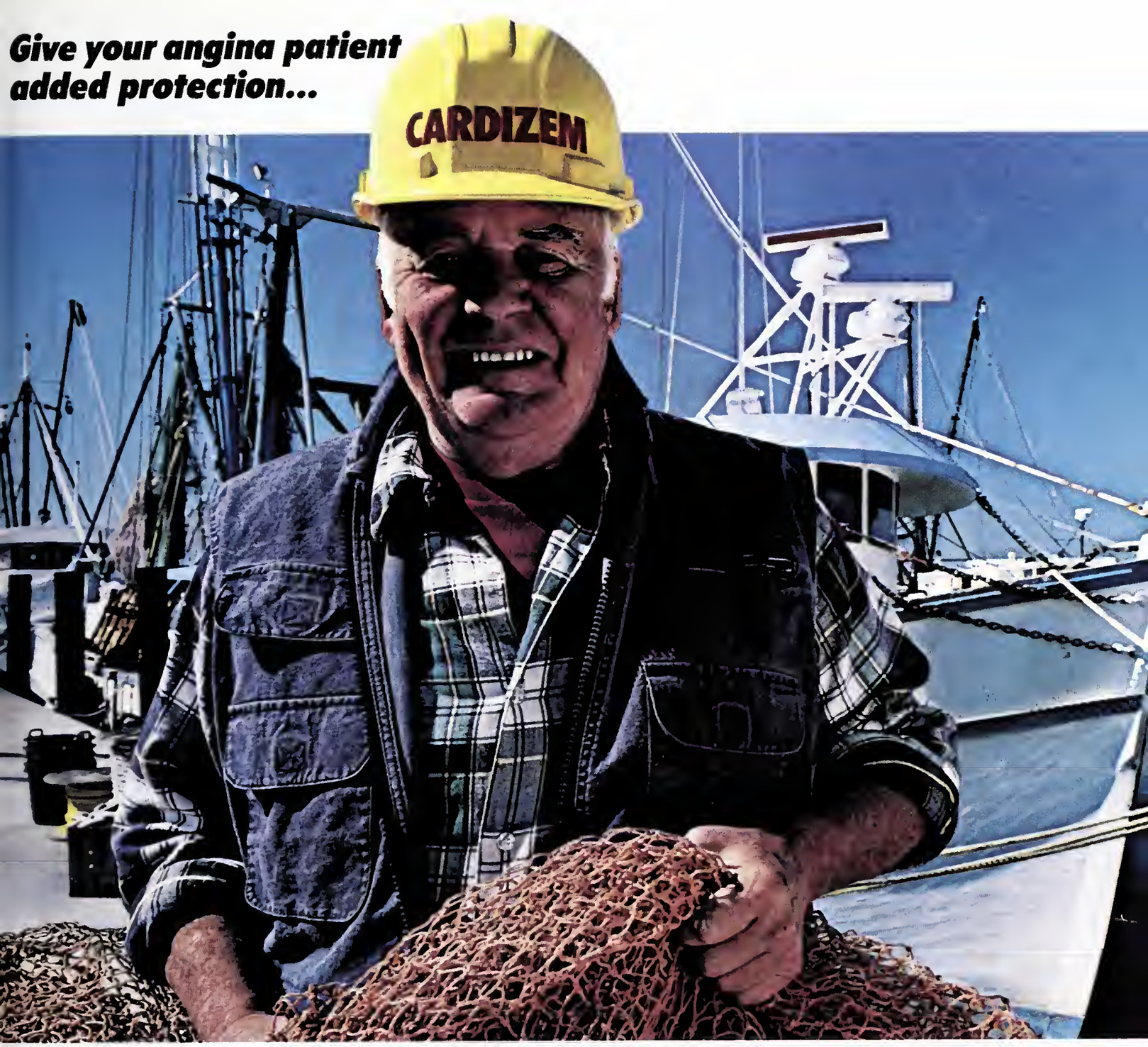
September 1-5—**Physics and Biology of Radiology.** UCSD at Town and Country Hotel, San Diego. Monday-Friday. 28 hrs. Contact: R. Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

September 6—**Radiology.** Kaiser Permanente Medical Group at Disneyland Hotel, Anaheim. Saturday. 7.5 hrs. Fee: $100. Contact: Judy Harrison, Dept of Clinical Services, Southern California Permanente Medical Group, 393 E Walnut St, Pasadena 91188. (818) 405-5000.

September 6-7—**Head and Neck Radiology.** UCSF at San Francisco Hyatt Regency. Saturday-Sunday. Contact: UCSF.

(Continued on Page 31)

Give your angina patient added protection...



CARDIZEM®: FEWER SIDE EFFECTS

diltiazem HCl/Marion

- ***The lowest incidence of side effects among the calcium channel blockers[1]***
- ***An exceptionally safe choice for angina patients with coexisting hypertension, diabetes, asthma, or COPD[1-3]***
- ***Proven efficacy when used alone in angina[1, 4-6]***
- ***Compatible with both beta-blockers and nitrates[7]***

Please see brief summary of prescribing information on the next page.

CARDIZEM® 60 mg tid or qid

diltiazem HCl/Marion

FEWER SIDE EFFECTS IN ANTIANGINAL THERAPY

BRIEF SUMMARY

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist)

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic)

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM (diltiazem hydrochloride) in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity
Other	Polyuria, nocturia

The following additional experiences have been noted.

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered.

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy** — CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

CARDIZEM 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARIDN on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARIDN on one side and 1772 on the other. Issued 4/1/84

See complete Professional Use Information before prescribing.

0642T5

References: 1. *Physicians' Desk Reference®* ed 39. Oradell, NJ, Medical Economics Company Inc, 1985. 2. Cohn PF, Braunwald E. Chronic ischemic heart disease, in Braunwald E (ed). *Heart Disease: A Textbook of Cardiovascular Medicine*, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39. 3. Schroeder JS. Calcium and beta blockers in ischemic heart disease: When to use which. *Mod Med* 1982; 50(Sept):94-116. 4. Subramanian VB. Comparative evaluation of four calcium antagonists and propranolol with placebo in patients with chronic stable angina. *Cardiovasc Rev Rep* 1984; 5:91-104. 5. Schroeder JS, Feldman RL, Giles TD, et al: Multiclinic controlled trial of diltiazem for Prinzmetal's angina. *Am J Med* 1982; 72:227-231. 6. Weiner DA, McCabe CH, Cutler SS, et al. The efficacy and safety of high-dose verapamil and diltiazem in the long-term treatment of stable exertional angina. *Clin Cardiol* 1985; 7:648-653. 7. Shapiro W. Calcium channel blockers: Actions on the heart and uses in ischemic heart disease. *Consultant* 1984; 24(Dec):150-159.

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(Continued from Page 28)

September 8-12—**Clinical Magnetic Resonance Imaging.** UCSF at San Francisco Hyatt Regency. Monday-Friday. Contact: UCSF.

September 12-14—**Sonographers' Update and Review.** UCSD at Hanalei Hotel, San Diego. Friday-Sunday. Contact: R. Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

September 24-26—**Interventional Radiology Tutorial: Non-Vascular Techniques.** Sharp Memorial Hospital, San Diego at Hyatt Islandia, San Diego. Wednesday-Friday. Contact: Elizabeth Douglas, Seminar Coordinator, 7901 Frost St, San Diego 92123. (619) 541-3206.

October 6-10—**11th Annual San Diego Postgraduate Radiology Course.** UCSD at the Hotel Del Coronado, San Diego. Monday-Friday. 24 hrs. Fee: $425. Contact: R. Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

October 10-11—**OB/GYN Ultrasound and Sonography—Update.** Sacramento Radiology Research and Education Foundation and Northern California Radiology Society. Friday-Saturday. 10 hrs. Fee: $125. Contact: John P. McGahan, MD, Sacramento Radiology Research and Education Foundation, PO Box 19184, Sacramento 95819.

October 19-23—**11th Annual International Body Imaging Conference.** West Park Hospital at Kauai, Hawaii. Sunday-Thursday. Contact: 11th Annual Body Imaging Conference, 21915 Roscoe Blvd, Ste 222, Canoga Park 91304. (818) 701-5143.

October 25-29—**Radiology.** USC at Kauai, Hawaii. Saturday-Wednesday. 27 hrs. Fee: $535. Contact: USC.

October 30-November 1—**San Diego Imaging Symposium.** UCSD at US Grant Hotel, San Diego. Thursday-Saturday. Contact: R. Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

November 3-7—**Diagnostic Radiology Seminars.** UCSF at Maui Marriott Hotel, Hawaii. Monday-Friday. Contact: UCSF.

December 11-13—**Advanced Ultrasound.** American College of OB/GYN at Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. 16 hrs. Contact: ACOG, 600 Maryland Ave SW, Ste 300 East, Washington, DC 20024-2588. (202) 863-2542.

SPORTS MEDICINE

August 14-16—**Cardiovascular Fitness/Sports Medicine.** Mercy Medical Center, Redding at Klamath River (rafting trip). Thursday-Saturday. 10 hrs. Fee: $125. Contact: Shelley Underwood, Inservice Education, PO Box 6009, Redding 96099. (916) 225-6171.

August 16-23—**Effective Diagnosis of Common Sport Injuries.** University of Arizona at Otter Bar Lodge, Forks of Salmon (near Eureka). One Week. Contact: Epic Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

November 25-28—**Sports Medicine.** American College of Sports Medicine and Children's Hospital Medical Center, Oakland at Inter-Continental Hotel, Maui. Tuesday-Friday. 25 hrs. Fee: $300. Contact: Stuart Zeman, MD, Course Chairman, 2999 Regent St, Ste 203, Berkeley 94705. (415) 540-8686.

SURGERY

September 27-October 4—**Temporal Bone Surgical Dissection and Cochlear Implant.** Los Angeles House Ear Institute. One Week. 62 hrs. Fee: $900. Contact: Antonio De La Cruz, MD, House Ear Institute, 256 South Lake St, Los Angeles 90057. (213) 483-4431.

September 28-October 1—**Preparing Patients for Surgery.** American College of Physicians and UCD at Monterey Hyatt Regency. Sunday-Wednesday. 14.75 hrs. Contact: ACP, Maxine Topping, (800) 523-1546, ext 207.

October 11—**Lumbar Spine and Pelvis.** UCSD at the Hotel Del Coronado, San Diego. Saturday. 7 hrs. Fee: $150. Contact: R. Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

October 18-19—**1986 Regional Review Course in Hand Surgery.** American Society for Surgery of the Hand at Orthopaedic Hospital, Los Angeles. Saturday-Sunday. 12 hrs. Fee: $200. Contact: American Society for Surgery of the Hand, 3025 S Parker Rd, Ste 65, Aurora, CO 80014. (303) 755-4588.

October 18-25—**Temporal Bone Surgical Dissection and Cochlear Implant.** House Ear Institute, Los Angeles. One Week. 62 hrs. Fee: $900. Contact: Antonio De La Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

October 24-26—**The Practical Applications of Recent Advances in Neurosurgery Research.** Scripps Clinic and Research Foundation, La Jolla. Friday-Sunday. 16.5 hrs. Fee: $250. Contact: Dept of Academic Affairs, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

November 1-8—**Temporal Bone Surgical Dissection and Cochlear Implant Courses.** House Ear Institute. One week. 62 hrs. Fee: $900. Contact: Antonio De La Cruz, MD, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

November 10-14—**Cochlear Implant.** House Ear In-

stitute. Monday-Friday. 32 hrs. Fee: $1,350. Contact: Antonio De La Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

December 4-7—**2nd Annual Fracture Management Symposium.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Thursday-Sunday. 18 hrs. Fee: $475. Contact: UCD.

December 7-19—**Temporal Bone Surgical Dissection and Cochlear Implant.** House Ear Institute. Sunday-Friday. 100 hrs. Fee: $1,700. Contact: Antonio De La Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

OF INTEREST TO ALL PHYSICIANS

July 25-26—**AIDS/ARC: Update '86.** UCSF. Friday-Saturday. Contact: UCSF.

August 10-16—**6th Annual Symposium on Fine Needle Aspiration.** UCSF at Sheraton at Fisherman's Wharf, San Francisco. Sunday-Saturday. 25 hrs. Fee: $550. Contact: UCSF.

August 16-27—**Hawaii Refresher Course.** USC at Honolulu/Maui. Saturday-Wednesday. 37 hrs. Fee: $535. Contact: USC.

August 21-22—**General Medicine for Practicing Physicians Update.** Northern Inyo Hospital at Bishop. Thursday-Friday. 10 hrs. Fee: $75. Contact: Mrs Barbara Parcher, Northern Inyo Hospital-Medical Education Bldg, 150 Pioneer Lane, Bishop, CA 93514.

September 9-10—**Developing Services for Comprehensive AIDS Care: San Francisco General Hospital Workshop.** UCSF. Tuesday-Wednesday. Contact: UCSF.

September 11-13—**What the Clinician Should Know About the Treatment of Chemical Dependencies.** California Society for the Treatment of Alcohol and Other Drug Dependencies at Marriott Hotel, Los Angeles Airport. Thursday-Saturday. 15-18 hrs. Fee: $350-400. Contact: Sandy Swift, 3803 Broadway, Ste 2, Oakland 94611. (415) 428-9091.

September 17-19—**Spine Update: 1986.** UCSF at San Francisco Hyatt Regency. Wednesday-Friday. Contact: UCSF.

September 19-20—**Progress in Impotence: Diagnosis and Therapy.** UCSD at Hotel Inter-Continental, San Diego. Friday-Saturday. 13 hrs. Fee: $295. Contact: UCSD.

September 18-21—**California Conference on Applied Clinical Geriatrics.** UCD at Yountville Veterans' Home, Napa Valley. Thursday-Sunday. Contact: UCD.

September 18-21—**Making a Difference: A Workshop for International Health Volunteers.** Plastic Surgery Foundation of San Diego at San Diego Hilton Beach and Tennis Resort. Thursday-Sunday. Fee: $125. Contact: Plastic Surgery Foundation of San Diego, PO Box 33387, San Diego 92103. (619) 692-9115.

September 24-26—**Primary Care Medicine: Principles and Practice.** UCSF at Golden Gateway Holiday Inn, San Francisco. Wednesday-Friday. 19.5 hrs. Fee: $350. Contact: UCSF.

October 4-11—**Effective Diagnosis and Treatment of Infectious Diseases: California Wine Country Bicycling Tour.** University of Arizona at Guerneville. One Week. 24 hrs. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

October 15—**Alcohol and Drug Dependency.** Kaiser Permanente Medical Group at Long Beach Hyatt Hotel. Wednesday. 6 hrs. Fee: $100. Contact: Judy Harrison, Dept of Clinical Services, Southern California Permanente Medical Group, 393 E Walnut St, Pasadena 91188.

October 17-19—**Practical Gastroenterology and Flexible Sigmoidoscopy for the Practicing Physician.** UCSD and Continuing Medical Education Associates at Vacation Village Resort, San Diego. Friday-Sunday. 20 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

October 22—**Update on Diabetes.** Hospital of Good Samaritan, Los Angeles at Moseley-Salvatori Conference Center, Los Angeles. Wednesday. 7 hrs. Contact: Dolores Gay, 616 S Witmer St, Los Angeles 90017. (213) 977-2352.

October 23-25—**International Conference.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. Contact: UCSF.

October 23-25—**Postgraduate Institute for Monterey Counties.** CMA at Sheraton, Monterey. Thursday-Saturday. Contact: Janice Rigney, CMA.

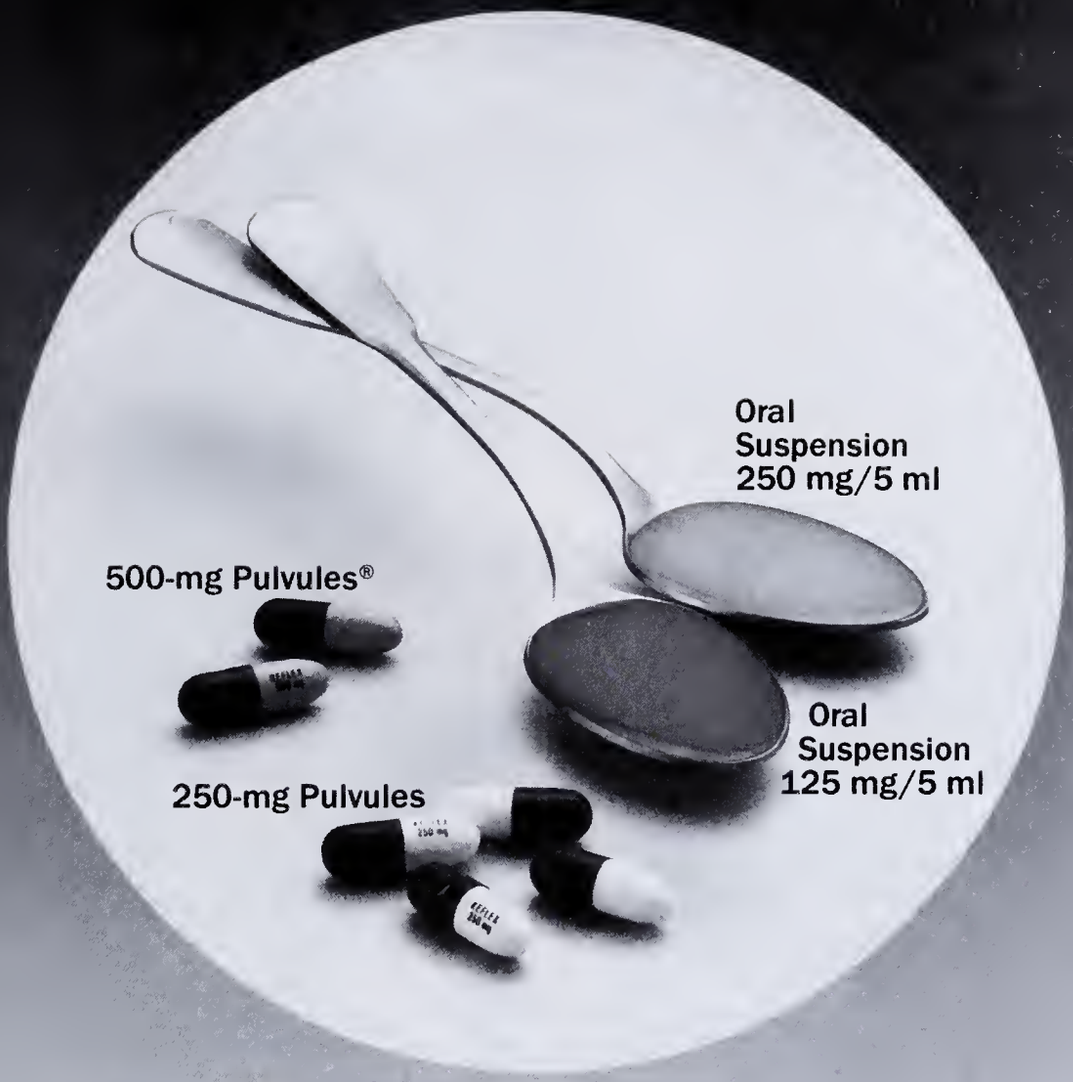
November 5—**Common Musculo-Skeletal Problems.** Veterans Administration Medical Center, Sepulveda. Wednesday. 5 hrs. Contact: Arun J. Mehta, MD, Rehabilitation Medicine Service (117), VAMC, Sepulveda 91343. (818) 891-2473.

November 14—**22nd Annual California Medical Center Staff Seminar: New Concepts in Medicine.** Los Angeles. Friday. 6 hrs. Fee: $50. Contact: California Medical Center, Kenneth L. Senter, MD, 1414 S Hope St, Los Angeles 90015. (213) 742-5750.

November 14-16—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital and Continuing Medical Education Associates at Hotel Del Coronado, San Diego. Friday-Sunday. 18

(Continued on Page 36)

Easy To Take



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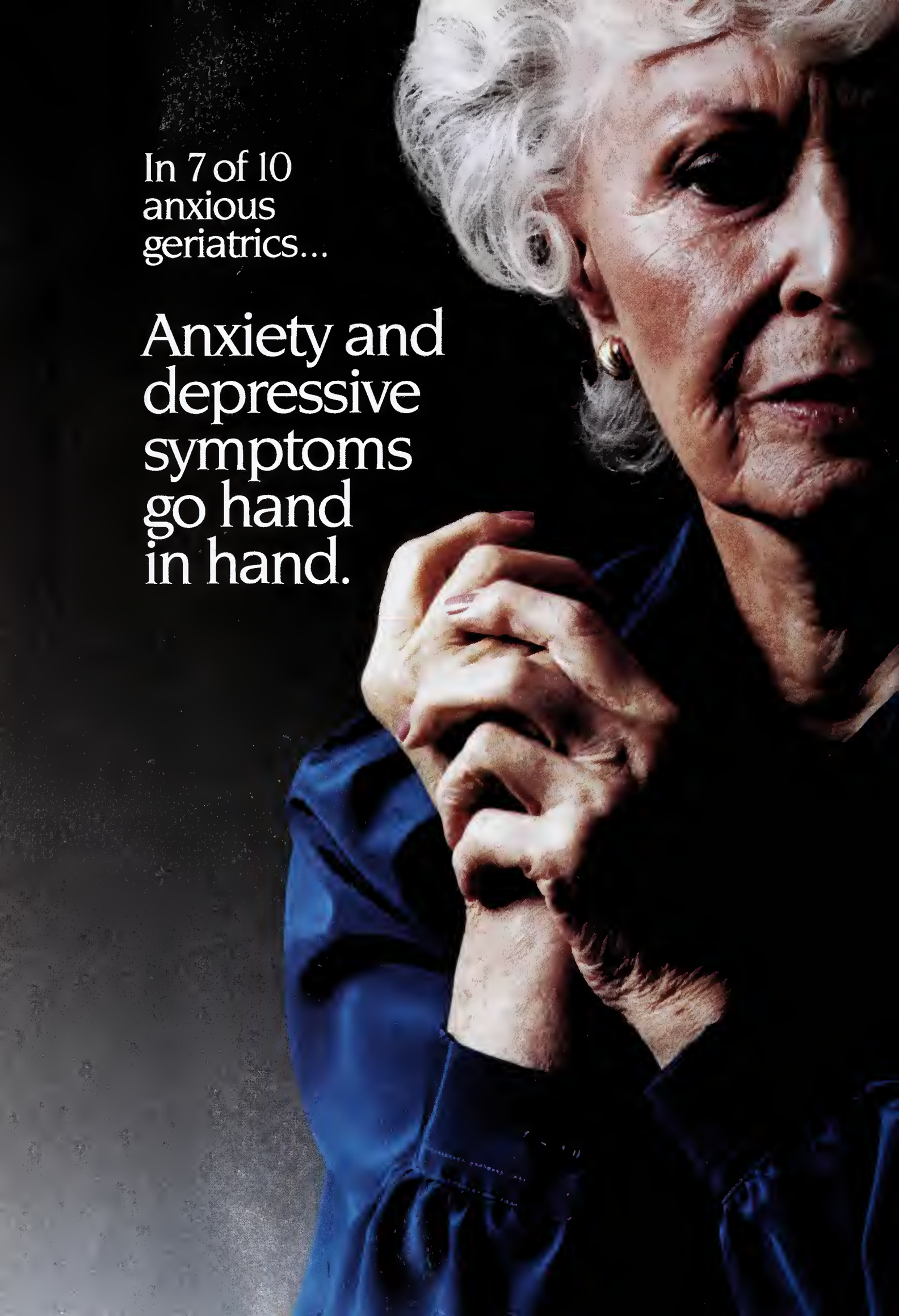
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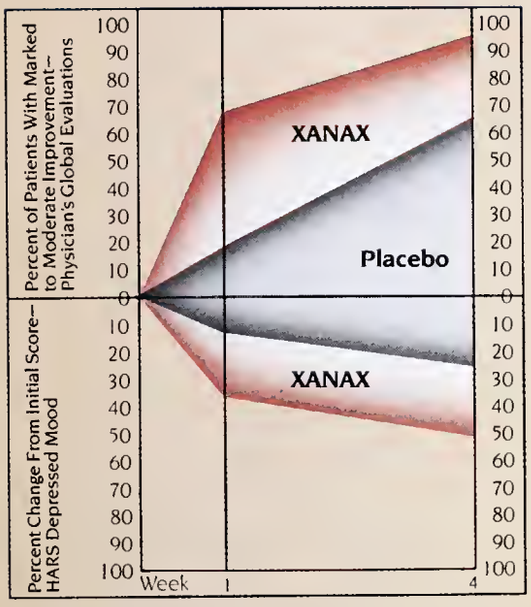

In a recent clinical study[1] of 83 geriatric patients with clinical anxiety, 73% were diagnosed as having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than does placebo in reducing the Hamilton Anxiety Rating Scale Total Score and individual items, including depressed mood (see Figure).

With clinical advantages for geriatric patients.

- Effectively relieves the symptoms of anxiety
- Also relieves anxiety with associated depressed mood
- Well tolerated—side effects, if they occur, are generally observed at the beginning of therapy and usually disappear with continued medication. Drowsiness and light-headedness were the most commonly reported adverse reactions
- Does not cause cardiovascular toxicity
- **Specific geriatric dosage**—0.25 mg, two or three times daily

1. Cohn JB. Double-blind safety and efficacy comparison of alprazolam and placebo in the treatment of anxiety in geriatric patients. *Curr Ther Res* 1984;35(1):100-112.

Xanax® 0.25 mg Tablets

alprazolam C-IV

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Kalamazoo, Michigan 49001, USA

Please see adjacent page for brief summary of prescribing information

XANAX® Tablets
(alprazolam) ℞

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, eg, drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes of unknown significance have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 32)

hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

November 21—**Orthopedic Symposium.** Kaiser Permanente Medical Group at Marina Beach Hotel, Marina Del Rey. Friday. 7 hrs. Fee: $100. Contact: Judy Harrison, Dept of Clinical Services, Southern California Permanente Medical Group, 393 E Walnut St, Pasadena 91188. (818) 405-5000.

November 22-29—**Stress Management: Hawaiian Islands Cruise Adventure.** University of Arizona. One Week. 24 hrs. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

December 11-12—**AIDS and the Nervous System.** UCSF at St Francis Hotel, San Francisco. Thursday-Friday. 10 hrs. Contact: UCSF.

IDAHO

July 23-26—**Idaho Medical Association—Annual Meeting.** Sun Valley. Wednesday-Saturday. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

August 1-3—**Coeur d'Alene Emergency Medical Conference.** Coeur d'Alene. Friday-Sunday. Sponsors: Idaho EMS System, Idaho ACEP, Idaho ACS and Rural Model EMS System. Contact: Lake Coeur d'Alene Emergency Conference, c/o Idaho EMS System, 450 W State St, Boise 83720. (208) 334-4245.

August 2-9—**Updates in Trauma.** Idaho Backcountry Bicycling Adventure. One week. Sponsors: University of Arizona, Department of Family and Community Medicine, and Epic Medical Expeditions. 24 hrs. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley 83353. (208) 788-4995.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 17-18—**Farwest Image Perception Conference.** Albuquerque. Thursday-Friday. Hilton Hotel. AMA

Cat. 1. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

July 21-24—**Ruidoso Family Practice Seminar.** Ruidoso. Monday-Thursday. Inn of the Mountain Gods. AMA Cat. 1, AAFP Prescribed Hours. Contact: NM Chapter, American Academy of Family Physicians, PO Box 23070, Albuquerque 87192. (505) 298-5300.

July 21-28—**Social Justice and Health Care.** Abiqui. One week. Ghost Ranch. Contact: Ghost Ranch, Abiqui, NM. (505) 685-4333.

July 24-26—**Update in Surgical Pathology.** Albuquerque. Thursday-Saturday. Sheraton Old Town Inn. AMA Cat. 1. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

July 25-26—**Santa Fe Cardiology Symposium.** Santa Fe. Friday-Saturday. Hotel Eldorado. 14 hrs. Cat. 1. Contact: Richard D. Lueker, MD, 3620 Wyoming NE, #114, Albuquerque 87111. (505) 292-1114.

September 11-13—**Concepts and Controversies in Perinatal Care.** Albuquerque. Thursday-Saturday. Clarion Four Seasons. AMA Cat. 1. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

September 20—**NM Physicians Mutual Liability Insurance Company Annual Loss Control Seminar.** Albuquerque. Saturday. Convention Center. Contact: K.D. Dickson, NMPMLIC, 303 San Mateo NE, Albuquerque 87108. (505) 262-1941.

September 26—**John N. Wilson, MD, Lectureship in Cardiovascular Disease.** Albuquerque. Friday. Marriott Hotel. 6 hrs. Cat. 1. Contact: Ann Nelson, Presbyterian Heart Institute, PO Box 26666, Albuquerque 87125. (505) 841-1438.

October 10-11—**Second Annual Balloon Fiesta Lung Disease Conference.** Albuquerque. Friday-Saturday. Contact: NM Chapter, American Thoracic Society, 216 Truman NE, Albuquerque 87108. (505) 265-0732.

October 10-12—**New Mexico Pediatric Association—Behavioral Disorders, Adolescent Adjustment Reaction, Sexual Abuse of Pre-adolescents.** Friday-Sunday. AMA Cat. 1. Contact: Charles Anderson, MD, PO Box 6132, Taos 87571. (505) 758-8651.

November 7-8—**New Mexico Medical Society Interim Meeting.** Las Cruces. Friday-Saturday. Holiday Inn de Las Cruces. Contact: New Mexico Medical Society, 303 San Mateo NE, Albuquerque 87108. (505) 266-7868

December 4-6—**Annual Meeting—New Mexico Chapter, American College of Physicians/New Mexico Society of Internal Medicine.** Thursday-Saturday. AMA Cat. 1. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave, Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 W Harvard Ave, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 W Harvard Ave, Roseburg 97470. (503) 673-6641.

Emanuel Hospital, 2801 N Gantenbein St, Portland 97227:

Every Friday, 12:15 p.m. to 1:00 p.m. **Medical Grand Rounds.** Contact: Philippa McClure, Emanuel Hospital, 2801 N Gantenbein St, Portland 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Ave, Portland 97210:

Every Tuesday, 12:00 noon to 1:00 p.m. **Medicine Grand Rounds.** Neurological Sciences Buildings, First Floor Auditorium. Contact: Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Ave, Portland 97201. (503) 229-7454.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder St, Eugene 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact:

(Continued on Page 134)

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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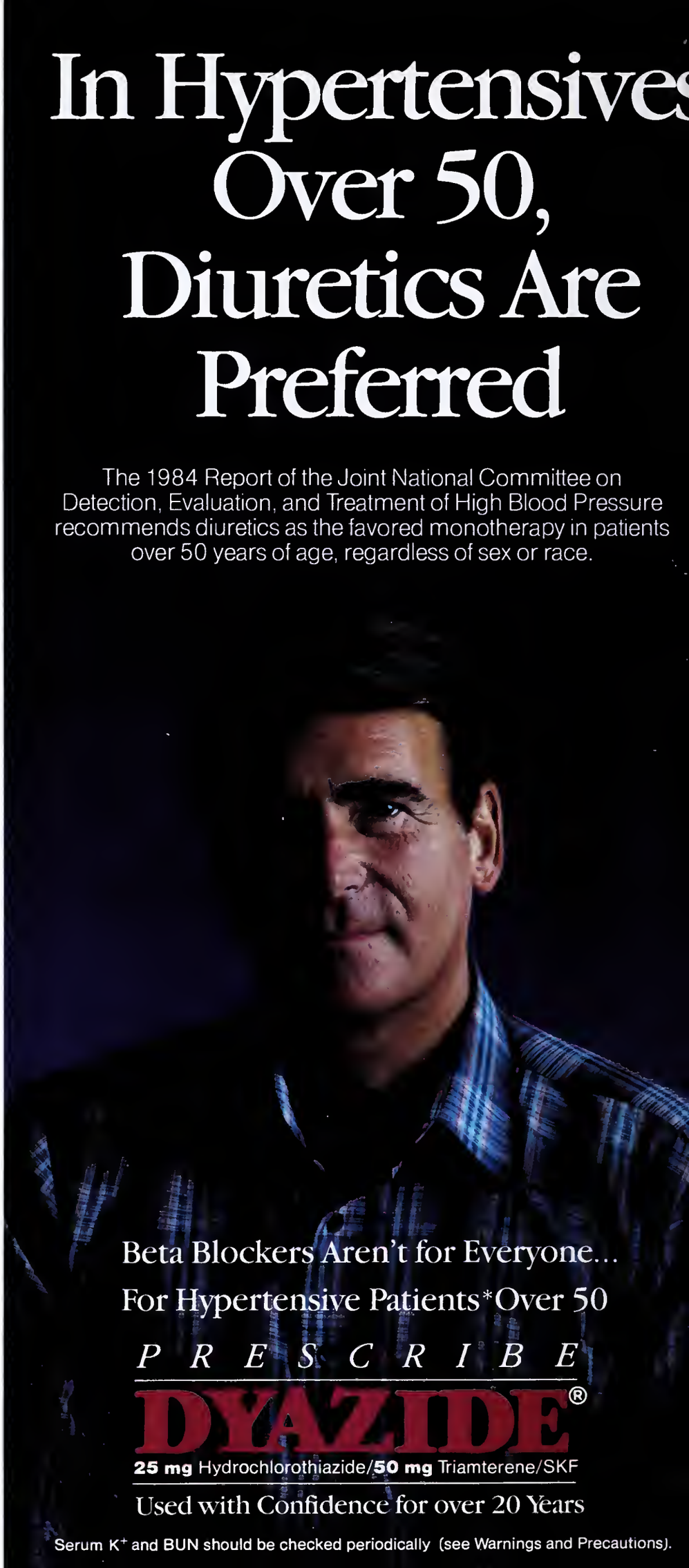

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Greater Vertebral Bone Mineral Mass in Exercising Young Men

JON E. BLOCK, PhD; HARRY K. GENANT, MD, *and* DENNIS BLACK, MA, *San Francisco*

Peak bone mass at skeletal maturity may be an important factor in the relative quantity of skeletal mass in old age. We have studied bone mineral in 46 young men, 28 of whom engage in regular and vigorous exercise programs. Spinal trabecular bone mineral density and spinal integral bone mineral content are significantly greater in the exercise group as compared with the 18 control subjects. Of the exercise group, subjects participating in both aerobic and weight-bearing regimens have the greatest spinal bone mineral mass, followed by those engaging in strictly weight-bearing exercise and those in a primarily aerobic program. An analysis of variance across all subject groups, including the control group, shows a significant difference in spinal trabecular bone density based on the type of physical activity.

(Block JE, Genant HK, Black D: Greater vertebral bone mineral mass in exercising young men. West J Med 1986 Jul; 145:39-42)

The continuous medical and public health efforts to reduce the occurrence of infectious and other fatal diseases have acted, in part, to reshape the national demographic structure.[1] As a result of an overall increase in the number of elderly persons, chronic diseases have emerged as the primary cause of disability and death.[2] Among the more prevalent of these conditions is osteoporosis as it primarily strikes older age groups.

Most research over the past two decades on osteoporosis and other age-related skeletal changes has focused on the histomorphometry, pathogenesis and physiology of this condition and, most recently, on the development of therapeutic interventions.[3-6] An increase, however, in the number of osteoporotic fractures commensurate with the expected demographic trend demands further attention to preventive strategies to combat this syndrome.

One possible strategy is to increase "peak" bone mass and strength in the young population. Types of exercise programs, as well as intensity and duration of exercise, have not been well studied or described in research dealing with skeletal health. Nevertheless, research to date has shown weight-bearing exercise to have positive effects on increasing bone mass regionally.[7-9] Aerobic forms of exercise such as running and swimming are likewise thought to have positive effects.[10,11] A recent study in a middle-aged population has shown the amount of bone mineral to be as much as 40% greater in the trabecular bone of the spine when comparing long-distance runners with controls.[12] The assessment of the amount of bone mineral at this site is of particular importance because of its primary susceptibility to atraumatic fracture and its presumed responsiveness to external and metabolic stresses.[13,14]

We have measured the amount of the spinal bone mineral in regularly exercising young men using quantitative computed tomography (CT). Most of these men have been habituated to many years of strenuous activity. We compared our results with bone mass calculations from physically inactive men.

Methods

Subjects

We recruited for exercise and control subjects by using several techniques: placing notices in athletic organization newsletters, personally visiting health clubs and dispensing brochures among medical students and hospital employees. All responders were invited to participate in an initial clinic visit on a volunteer basis in which they completed a research questionnaire and at which their spinal bone material was quantitatively assessed using CT. The research questionnaire, divided into four sections, assessed physical activity levels, medical history, diet and various behavioral patterns. Inclusion in the study was based on age (20 to 31 years) and either a history of vigorous physical activity or relative sedentariness. Subjects whose level of exercise did not fall into either physical activity extreme were excluded. Blacks were excluded from the study because of their apparent resistance to osteopo-

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rotic fractures. Other exclusion criteria were a history of steroid usage, thyroid disorders, diabetes mellitus and other metabolic conditions known to affect skeletal status.

The exercise group consisted of 28 men who had participated in strenuous exercise programs for at least two years. The exercise group was further categorized as follows: vigorous aerobic exercise was defined as at least 40 miles per week of running or six hours per week of aerobic exercise classes. Vigorous weight-bearing exercise was defined as at least six hours per week of rigorous weight lifting either with "free" weights or resistant weight training. A combination regimen was defined as either six hours per week of aerobic or "circuit" weight training, or six hours total per week of weight-bearing exercise coupled with running, swimming or other forms of aerobic exercise.

The control group, consisting of 18 men, was selected based on the criteria of the absence of participation in organized team sports, varsity athletics, intramurals and active membership in a health or fitness club. No control subject was currently involved in a regular program of physical fitness.

Bone Mass Measurements

The techniques for vertebral mineral measurement using computed tomography have been described elsewhere.[15] Briefly, a localization system (computed radiograph) is used to define the region to be scanned, the first and second lumbar vertebrae. A 10-mm thick scan is taken at the midvertebral body of L-1 oriented parallel to the end-plates to determine trabecular bone mineral density. This scan is done at 80 kilovolts (peak) (kV[p])—that is, single-energy scanning. Additionally, 18 contiguous 5-mm thick scans are obtained at 80 kV(p) scanning from the top of L-1 to the bottom of L-2 to determine the measure of total integral bone mineral content. For trabecular density, the mean CT number, a measure of x-ray attenuation, is determined for a 3- to 4-ml volume within the vertebral body and referenced to a mineral-equivalent calibration standard scanned with the subject. Data are analyzed on a specially programmed off-line computer. Subject time for the scan is ten minutes and radiation exposure is about 150 mrem to a 10-cm portion of the torso, with less than 10 mrem gonadal dose. Reproducibility for the technique is 1.6% in normal, healthy subjects.[16] Peripheral measurements of cortical bone were not done on any participants in this study.

Two types of analyses were carried out: the standard trabecular bone density and total integral bone mineral content. The former reflects the density (mg per cc) of trabecular bone in the midportion of the vertebral body, whereas total integral bone reflects the mass (grams) of compact and trabecular bone contained in the entire vertebrae of L-1 and L-2. Total integral bone mineral content was also divided by vertebral size and expressed as a density measure (mg per cc) to account for intergroup and intragroup variation in vertebral size. Total integral bone mineral content was not determined in every subject due to technical problems or alterations in scanning protocols.

Data Analysis

Data were entered and analyzed using Statistical Analysis System (SAS) software on the IBM 4341 mainframe at the University of California, San Francisco, Medical Center. Statistical significance of mean differences was assessed using a two-sample *t* test for two group comparisons and a one-way analysis of variance for three or more group comparisons.

Results

Height, weight and age for all participants are given in Table 1. Because an effort was made to create a uniform age distribution in the two study groups, there was only a small difference in mean age (27.6 years versus 25.9 years) and any differences in bone mass among the groups would not be expected to reflect age-related changes in bone. Mean body weight was 2.3 kg greater in the exercise group; previous studies, however, have not shown an association between body weight and trabecular bone density as determined by quantitative CT.[15,17] The exercise study group, based on the type of exercise program, was further divided as follows: ten men engaged in an aerobic and "impact-loading" regimen (such as running), nine men did weight-bearing exercise (weight lifting) exclusively and nine men engaged in a program that combined weight bearing and aerobic exercises (circuit weight training).

A comparison of measurements of trabecular bone density, total integral bone mineral content, total integral bone density and vertebral size for both study groups is given in Table 2. Spinal trabecular mineral density was 14% greater in the exercise group compared with the control group (184.02 mg per cc versus 161.34 mg per cc, $P = .0001$). The measure of total integral bone mineral content for L-1 and L-2 vertebrae for 26 of the physically active men was 11% greater than for 11 of the controls. Active men had a value of 41.6 grams of total bone and sedentary controls had 37.5 grams ($P = .04$). The results for total integral bone density indicated that integral bone density was slightly greater in the exercise groups as compared with control men (258.3 versus 253.9 mg per cc) but this difference was not statistically significant ($P = .67$). Vertebral size was 10% greater in the exercise group (164.1 cc versus 148.6 cc), but this difference did not reach statistical significance ($P = .18$).

Mean trabecular bone density by exercise type is shown in Figure 1. Persons engaged in a program that used both weight-bearing and aerobic forms of exercise had a mean value of trabecular bone density of 197.3 mg per cc, whereas those engaging in purely weight-bearing regimens had a mean value of 183.1 mg per cc and the aerobic exercise group had a mean value of 172.9 mg per cc. Men in the control group were lowest with a mean value for trabecular bone density of 161.3 mg per cc.

An analysis of variance was used to test for a significant difference across all four groups—that is, control, aerobic, weight bearing and aerobic plus weight bearing. There was a significant difference between groups for trabecular bone density ($P = .0001$). Differences in total integral bone mineral (grams) and total integral bone density (mg per cc), however, were not significant.

Preliminary analysis of the study questionnaire indicated that no identifiable dietary differences existed between groups. Intake of dairy products was comparable among the groups and was estimated at about 800 mg per day using standard references for calcium-containing foods. Three subjects in the exercise study group, however, did consume greater amounts of calcium-containing foods (about 1,800 mg

per day). Various dietary or nutritional supplements, such as vitamins, were used with greater frequency in the exercise group, with 21 (75%) subjects consuming at least one multivitamin or 1,000 mg vitamin C per day, whereas five sedentary men (28%) used nutritional supplements on a regular basis. No participants supplemented their diets with either vitamin D or calcium compounds. No participants in the study, either exercisers or controls, currently smoked cigarettes or had a history of heavy drug or alcohol usage.

Discussion

Vertebral trabecular bone mineral density is 14% greater in the exercise study group than in the control population. The difference between the two study groups supports previous research showing greater regional bone mass at appendicular sites for exercisers versus nonexercisers.[7,10,11] Integral bone mineral content in the spine is also greater in the exercise group; the percentage difference between groups, however, is 11%, just reaching statistical significance. Research has shown that the trabecular bone envelope may be a more sensitive area for measurement due to a turnover rate that is eight times greater than for cortical bone.[4,15] The measure of integral bone by CT, moreover, is subject to a greater variability in the technique than the trabecular measurement and, therefore, may not sensitively indicate subtle physiologic differences between study populations. A relatively smaller difference (2%) in integral density occurring between groups indicates that the larger vertebral size in the exercise group directly affects the measure of total integral bone mineral. Consequently, our data would suggest a more thorough examination of the effects of various types of exercise on trabecular bone density and vertebral size to differentiate the independent effects on various bone compartments over time.

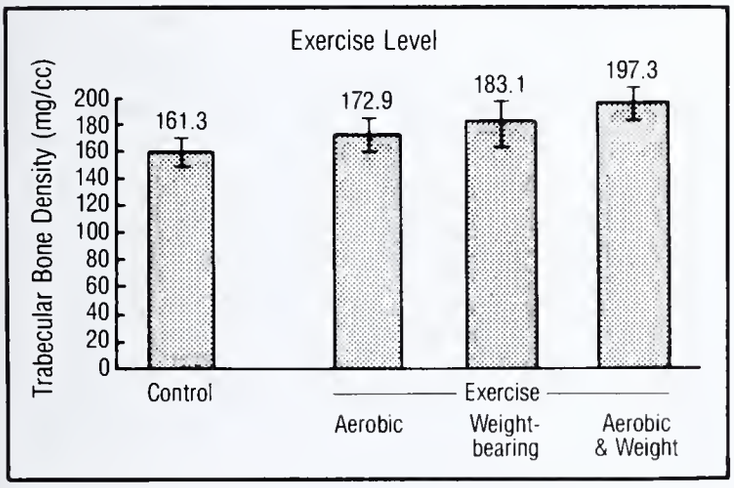

Figure 1.—This histogram, showing mean trabecular bone density by exercise level, shows progressively greater vertebral trabecular bone mineral through each exercise type.

Diet did not appear to be substantially different between groups, especially in regard to dairy products. The use of vitamins was a more common finding in the exercise group. Research to date, however, has not adequately assessed the effects of these nutritional supplements on skeletal mass.[18-20]

Little is known about the effects of different exercise regimens on skeletal mass. Our results show a differential response based on exercise type: the weight-bearing plus aerobic exercise group showed the greatest bone mineral mass and the purely aerobic exercise group showed the smallest increment in bone mineral mass. Interestingly, a general trend is apparent in our data that would support the hypothesis that lack of exercise may have adverse effects on the skeleton,[21] whereas a more comprehensive regimen combining weight-bearing and aerobic forms of exercise appears to be the most beneficial, with other forms of exercise falling in between (see Figure 1). An effort was made to compare groups according to similar amount of time spent exercising each week, and exercise duration was not found to be different between groups. It is difficult to determine from self-report data, however, if persons partaking in different regimens for a similar duration are doing so at comparable levels of intensity.

A bank of clinical normative data describing a general cross section of the normal population has been previously reported from our center.[22] Based on the limited data for men

TABLE 1.—*General Characteristics of Study Groups**

Study Group	*Age, yr*	*Height, m*	*Weight, kg*	*Exercise Type*
Exercise . . . . . (N = 28)	25.9 ± 3.5	1.79 ± 0.03	73.1 ± 2.7	. . .
A . . . . . (N = 10)	26.8 ± 3.6	1.80 ± 0.02	71.2 ± 2.3	Aerobic
B . . . . . (N = 9)	26.3 ± 3.7	1.78 ± 0.02	75.5 ± 3.4	Weight-bearing
C . . . . . (N = 9)	24.4 ± 2.8	1.78 ± 0.03	73.0 ± 2.5	Aerobic plus weight-bearing
Sedentary . . . . . (N = 18)	27.6 ± 2.1	1.78 ± 0.04	70.8 ± 3.4	None

*Mean ± standard deviation.

TABLE 2.—*Vertebral Measurements in Exercising Versus Sedentary Men*

Vertebral Measurements	*Study Group*		*Significance of Difference, P*
	Exercise	*Sedentary*	
	N = 28	N = 18	
Vertebral trabecular mineral, mg/cc	184.02 ± 18.7	161.34 ± 11.4	.0001
	N = 26	N = 11	
Vertebral integral mass, grams	41.61 ± 7.3	37.52 ± 4.3	.04
Vertebral size, cc	164.1 ± 29.8	148.6 ± 15.8	.18*
Vertebral integral density, mg/cc	258.28 ± 28.4	253.86 ± 29.3	.67*

*No significance.

aged 20 to 31 years (26 ± 3.3), the mean value for trabecular bone mineral density is 176.2 mg per cc (± 21.4). Specific information, however, concerning level of current or past physical activity, diet and behavioral habits was not collected in the generation of these normal values. Thus, data from this group could not be incorporated into our study in which these indices were well defined. The value of 176.2 mg per cc is 9% greater than the control group mean (161.2 mg per cc) and the difference is statistically significant ($P = .004$). This value is about 4% lower than that for the exercise group (184.0 mg per cc), but did not reach statistical significance ($P = .15$). These comparisons confirm what might be expected: the mean value of trabecular bone mineral of a cross section of the population would fall somewhere intermediately between a sedentary group and a highly active group. Preliminary work on a cross-sectional basis has indicated that varying degrees of exercise intensity may be reflected in a corresponding increase in spinal bone density.[23] Further research over the entire spectrum of physical activity should serve to clarify whether any increase or decrease in physical activity will alter bone mass or whether an upper or lower threshold exists.

Results of cross-sectional population studies all show that there is a significant loss of bone with normal aging and that this occurs throughout the skeleton.[13,22,24,25] Bone mass usually increases to a peak in the decade between ages 30 and 40, then falls off gradually in both men and women, with an accelerated loss at the menopause in women due to the loss of estrogen production. An analysis of bone mass as a function of age in cross-sectional studies suggests that the rate of bone loss with aging is independent of the initial amount of bone[22,26,27]; therefore, persons who have more bone early in life probably also have more bone later in life. Longitudinal studies of rapid bone loss after menopause or oophorectomy support this finding by showing percentage rates of loss in the spine independent of initial absolute values.[15]

Persons in our sample engaging in a regular and rigorous program of exercise have more vertebral bone mineral than control subjects. With cross-sectional data such as these, however, it is unclear whether this increment will be continuous throughout life or whether the effects of exercise are transient, and whether the pattern of increase observed in our sample is the same in other race-sex groups. Furthermore, we cannot exclude the possibility that those persons with higher trabecular bone density are more likely to be physically active initially based on their increased skeletal size. A further evaluation of our questionnaire data may prove useful in interpreting these issues.

The design and implementation of various exercise programs as effective prophylaxes against bone loss and consequent fractures have not been well described or investigated. In vitro studies have indicated a relationship between bone strength and fracture[28-30]; a paucity of information exists that addresses these areas in vivo, however, especially in relation to the effects of various forms and degrees of physical activity. Therefore, we must design and develop new noninvasive methods of assessing bone strength and structure in exercising and nonexercising populations as a way of complementing our present knowledge of determining bone mass. A number of opportunities now challenge the clinical and research communities. Longitudinal studies will be necessary in diverse study groups to determine the long-term effects of exercise intervention.

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Outpatient Treatment of Lumbar Disc Sciatica

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Of 47 patients with lumbar disc disease and sciatic radiculopathy (L-5 or S-1), 39 were successfully managed at home and as outpatients in an ambulatory care facility designed for the treatment of arthritis and back pain. When these patients were evaluated one to three years following discharge, they maintained their maximum level of activity and functional improvement noted at discharge. The average total cost per patient including physician's fees, x-rays, laboratory and therapy was approximately equivalent to the day rate for 1½ days in hospital.

(Swezey RL, Crittenden JO, Swezey AM: Outpatient treatment of lumbar disc sciatica. West J Med 1986 Jul; 145:43-46)

Each year 7 million Americans will join more than 75 million of their fellow Americans who have suffered low back pain and will spend more than $5 billion on tests and treatments for back pain, and 200,000 of them will undergo lumbar disc operations (*Time*, March 17, 1980, pp 30-38). The burden of the cost of medical care to which back pain treatment contributes so greatly has precipitated a major restructuring of the health care "industry," with a particular emphasis on the shift of inpatient to outpatient treatments whenever feasible.[1,2] Whereas most "low-back strains" are satisfactorily treated on an outpatient basis, the management of lumbar disc derangements with sciatic radiculopathy and the attendant risk of paralysis or unrelenting pain have made admission to hospital for two to three weeks of bed rest and conservative treatment the gold standard by which conservative treatments should be judged before intervening surgically.[3-12]

To assess the efficacy of ambulatory care for lumbar disc-related sciatica, we retrospectively evaluated the outcomes in 50 patients. All of these patients were seen at our ambulatory care facility and were followed for a period of at least one to three years after discharge from our center. These patients were chosen at random, the only criterion being the diagnosis of lumbar disc with sciatic radiculopathy in an L-5 or S-1 distribution. Patients were then reevaluated four to seven years after discharge from the center. The treatment program utilized a comprehensive programmatic approach to treat lumbar disc disorders in the center, which was designed specifically for ambulatory care management of arthritis and back pain and related rheumatologic conditions (see Tables 1 and 2).[13,14]

Patients and Methods

We initially selected for study 50 adult patients who met the clinical criteria for lumbar disc derangement with an L-5 or S-1 sciatica and who had been discharged from the center for at least one year. The clinical criteria for sciatic radiculopathy included an objective sensory or motor deficit on clinical examination and a positive straight-leg-raising test. (The criterion for positive straight-leg raising was the production of sciatic pain, numbness or tingling with or without back pain when the extended leg was raised 60 degrees or less from the horizontal.) In all, 46 patients had sensory deficits, of whom 21 had motor deficits as well. Two patients had motor deficits only. In eight patients, electromyographic (EMG) examinations substantiated the clinical evidence for motor deficits. Routine x-ray films of the lumbar spine were done on all patients. Evidence of discogenic spondylosis was noted in most cases, but no evidence of tumor, infection or fracture was found. Electromyography, computed tomographic (CT) scans and myelograms were not considered essential to the clinical diagnosis and were not done routinely.[7,15-17] All patients were evaluated by a structured telephone interview or from chart data at the time of follow-up. The follow-up evaluations were conducted by a physician (J.O.C.) who had not been responsible for the treatment of patients in this study. Three patients were eliminated from the original study group: two because they had had previous laminectomies and one apparently psychotic patient who refused psychological evaluation. Thus, 47 patients remained in the final study group.

Demographics

There were 29 male and 18 female patients, with a mean age of 47.1 years (range 26 to 73 years). One patient had had

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ABBREVIATIONS USED IN TEXT

CT = computed tomography
EMG = electromyogram

a chymopapain nucleolysis but was considered to have a separate episode of radiculopathy and was included in the study. The mean duration of symptoms before our initial evaluation for those requiring an operation was 9.5 months (range 6 weeks to 48 months). The mean duration of symptoms before our initial evaluation in the conservatively managed group was 5.5 months (range 2 days to 18 months). Eight patients had been treated in hospital before our initial evaluation for periods ranging from 1 to 3.5 weeks. Two of the eight patients were in the surgical group and had been previously treated in hospital, one for 1 week and one for 3.5 weeks. The patients were generally above average socioeconomically and, except for one patient who had a Workers' Compensation claim pending, were not involved in litigation. In none of the patients did evidence of cauda equinal compression develop during or after the initial therapeutic regimen.

TABLE 1.—*Diagnostic and Therapeutic Classification for Low Back Pain*

Chronicity
- Acute: 0-4 wk since onset
- Subacute: 4-12 wk since onset
- Chronic: 12 or more wk since onset
- Chronic, recurrent, unstable: Low back pain or sciatica (or both) of greater than 12 wk duration, which has worsened in the past 12 wk.
- Chronic, persistent, stable: Low back pain or sciatica (or both) of greater than 12 wk duration, which has not changed in character during the past 12 wk.

Severity
- Severe: Intense pain in the lumbar area (lumbago) or pain radiating into the leg (sciatica), or both, which is either continuous or provoked by almost any movement affecting the back and requiring narcotics or bed rest or both in a back-protected position for relief. Neurologic deficit (or positive straight-leg-raising test) of suspected or known recent onset with or without significant pain.
- Moderate: Less intense lumbago-sciatic pain usually precipitated by prolonged sitting, standing or sudden unguarded movement and requiring only several h bed rest, local heat or cold, mild analgesics or occasional narcotics for relief. If acute, no neurologic deficit is present. If subacute or chronic, any neurologic deficit is stable or regressing.
- Mild: Low back or sciatic pain or both is tolerable and usually intermittent and achy in character, precipitated by fatiguing or stressful activity such as driving for two or more h, prolonged standing, brisk walking or jogging more than 0.8 km (0.5 mi), carrying a full shopping bag for one or two blocks or typing for one hour. Pain is usually relieved with local heat or cold and short rests or mild analgesics.

Results

Of 47 patients with clinical signs and symptoms of acute to subacute L-5 or S-1 lumbar disc with radiculopathy, 39 were successfully managed in an outpatient treatment program. The patients when initially seen required bed rest or minimal activity for control of symptoms and were classified as phase I (bed rest) or phase II (part-time out of bed) (Tables 1 and 2).[14] At the time of the initial follow-up (one to three years after discharge), 37 of 39 of these patients were all in phase III (engaged in full-time sedentary work and home activity) or phase IV (engaging in vigorous sports) (Table 3).[14] The phases were used as a basis for scoring—that is, phase I = 1 and phase IV = 4. The initial mean score for the 47 cases was 1.4 ± 0.5, and the final score for the 39 patients not requiring a surgical procedure was 3.6 ± 0.7. Two patients made no improvement and refused an operation as well. One patient had a chymopapain nucleolysis and seven patients had laminectomies.

The mean duration of treatment in the 39 nonsurgical cases was 115 ± 76 days. The mean duration of treatment at the center before referral for an operation in the eight patients requiring either chymopapain or an operation was 38 days (with a range of 10 to 145 days). If the one patient with chronic recurrent symptoms who ultimately had a laminectomy is excluded, the time from the first visit to surgical referral averaged 23 days (range 10 to 36 days).

The average cost for total management of the nonsurgical cases at the center, including physicians' fees, physical therapy and occupational therapy, corsets and supplies and

TABLE 2.—*Functional and Therapeutic Classifications of Low Back Pain Syndromes*

Phase	*Activity*	*Definition*	*Exercise*
I	Bed rest 90%, up only for bathroom (and meals if not in pain when seated)	Severe acute, subacute and chronic with unstable recurrence	Simple stretching for pain relief and basic abdominal conditioning done with back protected
II	Up 10% to 90% of waking hours, daily activities modified to minimize back stress	Severe, chronic but stable; moderate acute, subacute chronic, and mild acute	Graduated lumbar, gluteal and thigh stretching with progressive abdominal and hip and knee strengthening to improve mobility and strength to facilitate proper body mechanics
III	Up 100%, normal daily activities without restriction and mild to moderate athletics	Mild subacute and chronic with mild but unstable manifestations	Continue progressive mobilization and strengthening to facilitate endurance and resiliency for normal activities
IV	Engaging in competitive athletics	All above patients in remission and with mild chronic stable disease	Conditioning for vigorous sports

TABLE 3.—*Lumbar Disc With Radiculopathy: 1- to 3-Year Follow-up of 47 Cases**

Treatment Groups	*Initial Status*	*Discharge Status*
Conservative outpatient treatment, successful, N = 39	Moderate to markedly impaired (N = 37)	Normal activity or athletics (N = 37)
Conservative outpatient treatment, failed, N = 10	Moderate to severely impaired (N = 10)	Chymopapain nucleolysis (N = 1); laminectomy (7); refused surgical treatment (2) (AMA)

AMA = against medical advice

*Telephone or chart review.

laboratory and x-ray studies, but exclusive of the occasional EMG or CT scan (typically done only in those patients referred for surgical treatment), was $1,062. The average cost for the eight patients referred for an operation was $633 before the referral. Thus, the total cost for outpatient treatment was less than the prevailing daily bed charges for 1½ days in hospital ($739 per day in California in July 1983; *CMA News*, July 19, 1983).

Nine patients who had been admitted to hospital within six months before beginning treatment at the center required a longer duration of treatment ($P < .009$), but this did not influence the ultimate favorable outcomes in these cases. Factors having no significance to the outcomes of treatment were previous accidents of any kind, severity of initial symptoms, chronicity, sex, the use of braces and corsets or the use of transcutaneous nerve stimulators.

Discussion

The natural history of both low back pain and lumbar disc disease with sciatica promises a favorable outcome without surgical intervention in the vast majority of patients.[3-12,18] This fact coupled with the unimpressive outcomes of an operation in many cases underlies the growing trend toward the conservative management of lumbar disc disorders. The issue becomes more complex once evidence of sciatic nerve compression is found because of the potential for more persistent and more disabling symptomatology to ensue in these cases.[4,8,18] With the exception of early intervention for cauda equina compression or rapidly progressive unilateral leg paresis, the indications for surgical treatment become questionable in all instances of disc-related lumbar radiculopathy.[3-5,11,18] Perhaps the best that can be hoped is a marginally shorter convalescence with no realistic hope that an operation will prevent recurrence or minimize disability.[3,5,12,18]

Granting that conservative treatment of lumbar disc disorders is initially mandatory in almost all cases, one can identify the single most important variable to be considered in the successful conservative treatment of such patients, and that is bed rest.[3-12,18] The standard for adequate conservative treatment before surgical consideration is two weeks of bed rest in hospital with or without pelvic traction.[3-12,18] At the current hospital bed charges of $700-plus per day, exclusive of physicians' fees, therapy and diagnostic studies, even two weeks of hospital care for conservative treatment is extremely costly (*CMA News*, July 19, 1983).[1] This cost becomes enormous when one considers that 200,000 backs are operated on each year and that this represents only 3% of the cases of back pain requiring treatment.[18]

The possibility of managing patients with lumbar disc derangement and sciatica as outpatients becomes increasingly more attractive as methods of instructing patients in strategies for home treatment are refined. This is of particular interest in our series when the lengthy duration of symptoms before our initial evaluation is considered. The mean duration of preceding symptoms in the surgical cases was 9.5 months (range 3 weeks to 48 months) and for the conservatively treated cases was 5.5 months (range 1 week to 18 months). The strategies for home treatment include detailed instruction in bed transfers, chair and car transfers, choice of seating, easily applied and correctly fitted lumbosacral corsets, home cold-pack therapy, providing hospital beds for home and raised toilet seats when necessary, the fitting and instruction in the use of canes in some instances and the use of moderate analgesic medication for only a few days, all of which contribute to successful outcomes. The close follow-up—one to two visits per week—in the first few weeks of treatment, with reassessment and appropriate modifications of therapy, plays a major role in the orchestration of the therapeutic options toward a successful outcome. One of the problems with bed rest as therapy is the failure to instruct patients on how to get in and out of bed safely, and this and other failings in patient education regarding activities and exercise may lead to a higher early failure rate for conservative treatment, even when this is carried out under hospital conditions.

In most of our cases, bed rest with bathroom privileges is required for less than two weeks, with activities (phase II to phase III) gradually resumed over the course of the first month or two (Tables 1 and 2). After the successful achievement of phase III level activities and exercises, further conditioning for more vigorous athletic endeavors is commenced, which may require an additional two to three months of supervised progression of exercise and conditioning for specific sports.

Patient education with good adherence to the treatment program in terms of activity level and exercise conditioning appears to play an important role in the outcome. At the initial follow-up period (one to three years after discharge), 83% of the patients were continuing their exercises. At the time of the four- to seven-year follow-up, these patients were either continuing their discharge exercise program or had substituted another appropriate regimen such as yoga.

In 4 of the 39 patients treated conservatively as outpatients, one to four epidural steroid injections appeared to play an important role in reducing symptoms enough to allow for the successful continuation of conservative outpatient treatment rather than referral for surgical intervention. In four of the seven patients requiring surgical treatment, who had also had epidural steroid injections, there was no response and the surgical referral was made. In one of the four patients initially successfully treated conservatively who had a late recurrence of symptoms (after three years of follow-up), a second course

TABLE 4.—*Lumbar Disc With Radiculopathy: 4- to 7-Year Follow-up of 36/47 Cases**

Conservative Outpatient Treatment Group (31/39 cases)	
Maintained improved status after discharge	7
Further improved status after discharge	20
Occasional mild low backache	5/20
Occasional mild leg ache or paresthesia	4/20
1 severe transient episode of low back pain	2/20
Improved sciatic manifestations but subject to	
Transient episodes of moderate low back pain	1
Chronic low back pain	1
Recurrence of sciatica	2
Treated successfully as outpatient (epidural blocks)	1
Treated with chymopapain—successful 1 yr postinjection	1
Surgically Treated Group (5/7 cases)	
Chymopapain	
Improved with occasional low back pain and leg cramps	1
Laminectomies	4
Pain-free	2
Improved with mild leg and low back pain	2

*Telephone or chart review

of three epidural steroid injections permitted resuming convalescence and return to a phase III and better activity level, such as playing regular singles tennis.

Symptoms associated with a poor prognosis and the institution of epidural blocks or surgical intervention were refractory pain either at rest or with limited activity (such as a sitting or walking tolerance of less than ten minutes) and a persistently positive straight-leg-raising test at less than 45 degrees. Of 8 patients in the surgical group, 4 had both sensory and motor deficits compared with 13/39 cases in the conservatively treated group. The extent of the initial sensory and motor deficit did not adversely prejudice the outcome of the conservatively treated cases, but patients with progressing motor deficits would have been excluded from this study.

At the four- to seven-year benchmark, 4 of the 31 patients were either unimproved (one patient had chronic low back pain) or were having recurrent episodes of back pain three to four times yearly (this occurred in one patient who was able to continue his activity level but required a corset and a transcutaneous nerve stimulator for pain control during exacerbations) (Table 4). One patient required a chymopapain nucleolysis and had a year's convalescence after nucleolysis before returning to phase III activities. This recurrence or failure in 4 of the 31 patients available for follow-up at four to seven years represents a 9% poor result and 3% failure rate (the patient requiring chymopapain nucleolysis), or an 88% success rate in those 31 of 39 patients who were available for follow-up. This compares more than favorably with the 80% rate of initial improvement and the 26% recurrence rate after surgical treatment cited in Rish's review of surgical outcomes in lumbar disc disease.[18] The results of this study should also give cause for reconsideration by those who recommend an operation to prevent recurrences of lumbar disc-related problems.

Another aspect of outcome is the ability to return to work and the time it takes to do so. In a large series from Kaiser Permanente, the average duration of convalescence after surgical treatment of lumbar disc disease before return to work was 84.3 days.[5] This was considerably longer than the 17.3 days average return to work time for our patients and was slightly shorter than the 115 ± 76 days required by our patients to reach their maximum level of function before their initial discharge (phase III or phase IV).[14] The differences may reflect social and vocational differences in the patient populations and, more important, may reflect our continued supervision of patients until they have reached their maximum level of athletic capability.

Conclusions

Conservative treatment for lumbar disc disease with sciatica has proved to be feasible in 8% to 28% of patients in several large series.[18] Conservative treatment of lumbar disc with sciatica today has come to mean that two weeks of supervised bed rest in a hospital have been provided to a patient before considering a surgical remedy. In our series, 47 patients with lumbar disc disease and sciatic radiculopathy were successfully treated at home and as outpatients in a specially designed center. Only 15% of these patients required surgical remedies, and 79% of the patients treated conservatively returned to normal or athletic activities. Outpatient management in a properly designed program can be at least as effective in terms of outcome as hospital-based conservative treatment or surgical intervention or both. The economic benefits of outpatient conservative management make it potentially the treatment of choice for most patients with lumbar disc disease and associated sciatic radiculopathy.

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The Pharmacology of Neonatal Resuscitation and Cardiopulmonary Intensive Care Part II—Extended Intensive Care

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An optimal outcome for a distressed newborn infant can be achieved only if immediate resuscitation is followed by appropriate cardiopulmonary intensive care. In the preceding article in this series, we provided recommendations for drug therapy during the initial resuscitation. When an infant is stable enough for transfer to an intensive care nursery, extended cardiopulmonary intensive care should be initiated. If the infant remains distressed, this may require drug therapy to improve cardiac output, either by enhancing cardiac performance (dopamine, dobutamine or epinephrine) or by reducing afterload (nitroprusside). Drugs that alter the distribution of the circulation may be required for infants with persistent hypoxemia due to pulmonary hypertension or congenital heart disease (tolazoline, nitroprusside, prostaglandin E_1), or with pulmonary congestion due to persistent patency of the ductus arteriosus (indomethacin). Infants with pulmonary disease may benefit from administration of agents that alter pulmonary function (furosemide, nitroprusside or neuromuscular blockers). Finally, treatment of the underlying disorder, with antibiotics or naloxone, for example, must not be neglected.

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After immediate injury or death of a distressed neonate has been averted by initial resuscitation, as described in Part I, extended intensive care may be required. Infants who recover promptly from the events leading to distress may subsequently require only observation and monitoring. Others will continue to require pharmacologic support to improve or maintain cardiac output, to alter the distribution of the circulation or to alter pulmonary function. Optimal management of these infants requires continuous invasive monitoring of central venous and arterial pressures, which is most readily done with umbilical venous and arterial catheters, as discussed in Part I.

Agents That Increase Cardiac Output

The initial resuscitation of a neonate should eliminate bradycardia (by assisted ventilation or administering epinephrine, isoproterenol hydrochloride or atropine sulfate), treat hypovolemia and correct metabolic disorders that impair myocardial function (acidemia, hypoglycemia and hypocalcemia). These problems may persist or recur, and it may be necessary to continue or repeat the therapeutic interventions started early in resuscitation, as described in Part I.

Agents That Enhance Myocardial Function

Even though cardiac output is primarily dependent on heart rate in a normal newborn,[1] it should not be concluded that cardiotonic drugs cannot increase the cardiac output of sick infants. Infants with myocardial injury—due to sepsis or asphyxia—or myocardial edema, as with hydrops, may achieve significant increases in stroke volume and cardiac output after administration of β-mimetic catecholamines. Infants with structural abnormalities of the heart, such as endocardial fibroelastosis or congenital cardiac malformations

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(especially ventricular hypoplasia) are much less likely to benefit. These drugs may reduce cardiac output in infants with hypertrophic cardiomyopathy (most common in infants of diabetic mothers), because of narrowing of the right ventricular infundibulum, and are contraindicated in this condition. Little benefit will be realized from enhanced myocardial function if either the heart rate or end-diastolic ventricular volume is inadequate, so infusion of dopamine hydrochloride or dobutamine hydrochloride is not appropriate until these conditions are corrected (as discussed in Part I). These drugs are ineffective if the systemic pH is below 7.1 and are inactivated by admixture with alkaline solutions.

Dopamine. The effects of dopamine in infants are dose-dependent and similar to those obtained in adults.[2-4] A recent report suggests that beneficial effects may occur at doses as low as 0.8 μg per kg per minute.[5] At 2 to 5 μg per kg per minute, dopaminergic receptor-mediated dilation of renal and splanchnic vessels causes increased glomerular filtration, urine output and urinary sodium excretion. β-Adrenergic effects, including improved cardiac contractility, a moderate increase in heart rate, mild peripheral vasodilation and increased cardiac output, are apparent with doses of 5 to 15 μg per kg per minute. At doses exceeding 20 μg per kg per minute, α-adrenergic effects become prominent, resulting in increased systemic vascular resistance and arterial blood pressures with reduced cardiac output and renal perfusion, but effects on the pulmonary vascular resistance and pulmonary arterial pressure are much less pronounced.[6]

The use of dopamine is primarily indicated (at 5 to 15 μg per kg per minute) for hypotension or impaired cardiac output resulting from poor myocardial function, but may also be useful (at 2 to 5 μg per kg per minute) to improve renal perfusion and urine output in infants with marginal cardiac output. Differential systemic vasoconstriction at 15 to 25 μg per kg per minute may be useful in the management of persistent pulmonary hypertension, particularly when combined with vasodilator infusion. Diluting 15 mg of dopamine per kg body weight to 250 ml in 5% or 10% dextrose in water provides a solution for which the rate of infusion in milliliters per hour equals the dose in micrograms per kilogram per minute, allowing rapid preparation and calculation of infusion rates.

Dopamine increases myocardial oxygen demands and may cause tachyarrhythmias. Excessive doses compromise perfusion of peripheral tissues, and striking vasoconstriction occasionally occurs even at low doses. Tissue necrosis due to severe local ischemia following extravasation can be prevented by prompt infiltration of phentolamine mesylate (0.5 to 1 mg) into the affected area.

Dobutamine. This selective β-adrenergic agent, which increases cardiac contractility and cardiac output and has minimal effects on heart rate and vascular tone,[7] is primarily used for cardiogenic shock refractory to dopamine infusion. The recommended dose is 2.5 to 15 μg per kg per minute, titrated to achieve the desired improvement in cardiac performance. Dobutamine is often added to rather than substituted for dopamine infusion, but it is not known whether the combination is any more effective than either drug alone. The drug may be less effective in infants younger than 12 months and in cases of shock due to sepsis.

Epinephrine. For cardiogenic shock unresponsive to other catecholamines, epinephrine infusion (0.5 to 1.5 μg per kg per minute) may be beneficial.[7] In most cases, however, the adverse effects of increased vascular resistance outweigh the benefits of increased contractility.

Agents That Reduce Afterload

With severely compromised myocardial function, the cardiac output may remain inadequate even with appropriate heart rate, preload and inotropic therapy. Vasodilator administration to decrease the systemic vascular resistance (afterload) reduces the pressure and ventricular wall tension required for ejection of blood from the ventricles into the great arteries, in effect, moving the Starling curve upwards and to the left[8] without affecting myocardial function itself. Therefore, increased cardiac output can only be expected in infants who have elevated systemic vascular resistance and normal or elevated blood pressure.

Nitroprusside. Cardiac output may increase (because of reduced afterload due to dilation of arterioles and precapillary sphincters), decrease (because of reduced preload due to increased venous capacitance) or be unchanged (because these effects are balanced) after nitroprusside infusion. Frequent assessment of cardiac output and continuous invasive monitoring of systemic arterial and central venous pressures during nitroprusside infusion are therefore essential. Moderate relative hypovolemia, which is masked by increased sympathetic tone and adrenal catecholamine release, may result in a sharp decrease in venous pressure when nitroprusside is infused, further reducing cardiac output and arterial pressure. This complication can usually be avoided by judicious expansion of the vascular volume (see Part I) in preparation for vasodilator therapy, but blood or plasma should always be immediately available when nitroprusside infusion is initiated.

A nitroprusside infusion should be started at 0.25 to 0.5 μg per kg per minute. The dose should be doubled every 15 to 20 minutes until the cardiac output and systemic perfusion improve, hypotension or excessive tachycardia supervenes or the dose reaches 6 μg per kg per minute.[9] After 12 to 24 hours of hemodynamic stability, the dose should be weaned as tolerated, in decrements of 15% to 25% at intervals of four to six hours, until it is reduced to 0.25 to 0.5 μg per kg per minute, when the infusion can be discontinued. Rebound hypertension during weaning may require moving in smaller decrements at more frequent intervals.

Cyanide and thiocyanate accumulate during prolonged infusion of nitroprusside, but toxic effects from therapeutic doses appear to be rare.[9] Measuring blood or plasma concentrations of these metabolites is primarily useful for detecting dosage errors, because there are no prospective data that correlate these levels with the risk for toxic effects. Cyanide intoxication causes histotoxic hypoxia, with elevation of the mixed venous oxygen saturation and persistent metabolic acidosis. Tachyphylaxis to the vasodilator effects of nitroprusside may be an early sign of cyanide toxicity. These findings obviously require immediate discontinuation of nitroprusside therapy. The possibility of toxicity necessitates persistent attempts to wean nitroprusside infusions, which cannot be justified unless a beneficial effect is demonstrable, even if metabolite levels are low. On the other hand, if the only alternative is severely compromised cardiac output or impaired cerebral perfusion, the benefit of therapy outweighs the unknown risks of metabolite accumulation.

Agents That Alter the Distribution of the Circulation

Drugs that facilitate or alter the crucial cardiovascular adjustments associated with the transition from the fetal to the neonatal circulation represent a unique aspect of resuscitation pharmacology of neonates, which has no counterpart in older children or adults. These agents reduce the pulmonary vascular resistance or control the patency of the ductus arteriosus.

Agents That Reduce Pulmonary Vascular Resistance

If the dramatic decrease in pulmonary vascular resistance that normally follows birth fails to occur, right-to-left shunting through the ductus arteriosus and foramen ovale causes severe hypoxemia. The primary therapies for these infants with persistent pulmonary hypertension are oxygen administration (to maintain a partial arterial oxygen pressure [Pa_{O_2}] above 100 mm of mercury), sedation and mechanical ventilation. Neuromuscular blockade and hyperventilation (to a partial arterial carbon dioxide pressure below 25 mm of mercury)[10] have been widely used, but good outcomes may be achieved without these interventions.[11] If these measures are insufficient, vasodilator therapy may be required. Preparation for vasodilator infusion should include expansion of the vascular volume and dopamine infusion (10 to 20 μg per kg per minute).

Tolazoline. Infusion of tolazoline hydrochloride, which has both histaminelike and α-adrenergic blocking effects, causes both pulmonary and systemic vasodilation. Tolazoline (1 to 2 mg per kg over ten minutes followed by infusion at 1 to 2 mg per kg per hour) resulted in an increment in the Pa_{O_2} of at least 20 mm of mercury in 87% of infants with persistent pulmonary hypertension, but this response did not correlate with survival, which was only about 50%.[12] Severe hypotension unresponsive to volume expansion may follow tolazoline infusion, especially in premature infants with the respiratory distress syndrome and infants with relative hypovolemia. Gastrointestinal or pulmonary hemorrhage, thrombocytopenia and tachyarrhythmias have been observed during tolazoline infusion.

Nitroprusside. Increments in Pa_{O_2} following nitroprusside infusion[9] for infants with persistent pulmonary hypertension were smaller and less consistent than those achieved following tolazoline[12] infusion in a similar group of infants. As with tolazoline, there was no correlation between these responses and outcome, and the mortality rate (about 50%) was identical. These results suggest that vasodilator therapy, at least as currently applied, may not alter outcome for infants with persistent pulmonary hypertension; a prospective randomized trial will be necessary to resolve this question. Because toxic effects were less common with the use of nitroprusside and outcomes were similar with both agents, nitroprusside is our first choice for vasodilator therapy for infants with persistent pulmonary hypertension. Administration of nitroprusside to these infants should follow the guidelines outlined for infants with compromised cardiac output.

Agents That Maintain Patency of the Ductus Arteriosus

Maintenance of ductal patency may be life-saving in infants with a variety of congenital cardiac malformations, including those in whom pulmonary blood must be derived from the aorta via the ductus arteriosus (because of right-sided heart obstruction), those in whom systemic perfusion is dependent on flow from the pulmonary artery through the ductus to the aorta (due to left-sided heart obstruction) and those in whom admixture of blood from the systemic and pulmonary circulations is essential for maintaining systemic arterial oxygen content (Table 1).

TABLE 1.—*Ductus-Dependent Cardiac Malformations*

Right-Sided Heart Obstruction
Tricuspid atresia
Pulmonary atresia or severe stenosis
Truncus arteriosus with ductus-dependent pulmonary arteries
Tetralogy of Fallot
Left-Sided Heart Obstruction
Coarctation of the aorta (preductal or juxtaductal)
Interruption of the aortic arch
Severe aortic stenosis
Mixing-Dependent Lesions
Transposition of the great arteries with an intact ventricular septum

Prostaglandin E_1. Selective dilation of the ductus arteriosus is achieved by administering a loading dose of 50 ng per kg (0.05 μg per kg) of prostaglandin E_1, followed by continuous infusion at 50 ng per kg per minute.[13] Once patency of the ductus is established, the dose can be gradually weaned to 10 to 20 ng per kg per minute. Infusion at higher rates causes pulmonary and systemic vasodilation, but other agents are probably preferable for these purposes. Prostaglandin E_1 administration has been associated with diarrhea, fever, tachyarrhythmias and systemic hypotension. Apnea may occur suddenly up to several hours after therapy begins and may require intubation and assisted ventilation. Seizures have also been reported during prostaglandin infusion but may result from hypoxemia preceding therapy rather than the drug.

Agents That Promote Closure of the Ductus Arteriosus

Persistent patency of the ductus arteriosus beyond the first 48 hours of life is often associated with shunting of blood from the aorta into the pulmonary artery, causing pulmonary congestion, increased interstitial lung fluid and congestive heart failure. This condition is more common in premature infants and is frequently associated with hyaline membrane disease. Early pharmacologic or surgical closure of the ductus in these infants improves pulmonary function, decreases the requirement for supplemental oxygen, shortens the period for which assisted ventilation is necessary and decreases the risk of chronic pulmonary disease.[14–16]

Indomethacin. Indomethacin promotes ductal closure by inhibiting production of prostaglandin E, the major endogenous mediator maintaining ductal patency. Indomethacin is most effective if given in the first few days of life and soon after ductal patency becomes clinically apparent. Ductal closure is more consistently achieved in premature infants with more than 1,000 grams birth weight than in smaller premature or term infants.

Prophylactic use of indomethacin in very-low-birth-weight premature infants (less than 1,000 grams birth weight) with cardiac murmurs has been suggested,[17] but ductal patency may not have significant hemodynamic consequences

(precordial hyperactivity, wide pulse pressure, tachycardia, tachypnea, hepatomegaly or increased respiratory distress) in 40% of these infants.[18] Infants with a patent duct should be managed with fluid restriction and diuresis for the first 48 hours, which is effective in about 25% of those with hemodynamic abnormalities. Indomethacin (0.25 mg per kg per intravenous dose) should be given to those infants who continue to have hemodynamic complications of ductal patency. If the duct remains patent 24 hours after the first dose, two additional doses should be given at 24-hour intervals; if it has closed, only one additional dose is necessary. If indomethacin therapy is ineffective or contraindicated, the hemodynamically significant patent duct should be closed by surgical ligation, which is 100% effective and associated with a low mortality and morbidity.

Glomerular filtration, urinary sodium excretion and urine output are decreased after administering indomethacin, but these effects may not be readily apparent in infants in whom renal function is already impaired by reduced blood flow due to ductal patency.[19] Administering furosemide concurrently with indomethacin may ameliorate these adverse effects but theoretically may also reduce the efficacy of indomethacin in blocking prostaglandin synthesis. Indomethacin should not be given to an infant with impaired renal function (blood urea nitrogen level more than 30 mg per dl or creatinine level greater than 1.8 mg per dl) or oliguria (urine output less than 0.6 ml per kg per hour in the preceding eight hours). Because platelet function is impaired by indomethacin, it should not be used in infants with a bleeding diathesis or a platelet count of less than 60,000 per μl. The incidence of necrotizing enterocolitis and focal gastrointestinal perforation, which have been associated with oral indomethacin use, may be substantially reduced if indomethacin is not used for infants with any clinical or radiographic evidence of gastrointestinal dysfunction. Similarly, the incidence of intracranial hemorrhage, which was increased in early studies, was not altered by indomethacin use in infants without evidence of intracranial bleeding within the preceding seven days.

Agents That Alter Pulmonary Function or Gas Exchange

Disorders of pulmonary function or gas exchange must be addressed primarily with oxygen administration (see Part I), continuous distending airway pressure or assisted ventilation, which will not be discussed here. Drugs that alter pulmonary function in neonates are limited to those that affect pulmonary mechanics by reducing pulmonary fluid content (furosemide and nitroprusside) or by reducing the effective pulmonary resistance (neuromuscular blockers).

Furosemide. In infants with elevated pulmonary venous and left atrial pressures, the use of furosemide (1 mg per kg per dose, up to four times a day) may improve pulmonary compliance by promoting reduction in the interstitial fluid content of the lungs. This effect is primarily a result of the decrease in vascular volume achieved by diuresis, but increased venous capacitance also contributes to reduced venous pressures, allowing translocation of pulmonary interstitial fluid to the venous system. Furosemide should be used only with great caution in infants with pulmonary edema due to compromised capillary integrity (postasphyxial or septic) in whom vascular volumes may already be reduced. The pulmonary function of these infants is unlikely to improve, and cardiac output may be compromised. Infants receiving more than an occasional dose of furosemide are at risk for hypokalemia, hyponatremia, hypochloremia and metabolic alkalosis. Long-term furosemide therapy may cause renal calculi, related to hypercalciuria.

Nitroprusside. Infusion of nitroprusside (1 to 2 μg per kg per minute) is associated with rapid (within an hour) improvement in arterial oxygen tensions and more gradual (over 12 hours) improvement in pulmonary compliance and carbon dioxide excretion in infants with severe hyaline membrane disease.[9] Improvement in PaO_2 appears to result from a reduction in right-to-left shunting through fetal channels, but the reasons for changes in pulmonary compliance are less readily evident. Decreased pulmonary arterial pressure following nitroprusside infusion may lead to reduced transpulmonary fluid filtration and thereby improve pulmonary mechanics. Vasodilator infusion may exacerbate hypoxemia in infants with nonuniform pulmonary parenchymal disease by increasing ventilation-perfusion mismatching or intrapulmonary shunting through unventilated units. These effects may account for the unpredictable effects of nitroprusside infusion in infants with pulmonary hypertension, many of whom have meconium aspiration syndrome.

Neuromuscular blockers. In infants with severe pulmonary disease, asynchrony between the infant's respiratory efforts and cycling of the mechanical ventilator or a large contribution of chest wall muscle tone to the total pulmonary resistance may make it virtually impossible to achieve adequate gas exchange. Administering pancuronium bromide (0.1 mg per kg per dose)[20] or metocurine iodide (0.2 mg per kg per dose)[21] every two to four hours as required to maintain neuromuscular relaxation may produce significant improvements in gas exchange and also may reduce the risk of pneumothorax. Both of these agents have weak atropinelike and histamine-releasing effects, which may cause reduced blood pressure, tachycardia and apparent increased skin perfusion. Neuromuscular blockade may increase the risk of intracranial hemorrhage. Neither drug is clearly superior for use in neonates. We recommend sedation with morphine sulfate (0.05 to 0.1 mg per kg every one to two hours) during neuromuscular blockade.

Agents That Treat the Underlying Condition

Although resuscitation and cardiopulmonary intensive care may be essential to survival of a distressed neonate, these are obviously inadequate if a life-threatening underlying condition remains untreated. These conditions represent much of the subject matter of neonatology, and it is impossible to address them comprehensively in a brief review. Two conditions for which pharmacologic therapies are quite effective, however, are worth noting. Because bacterial sepsis is a common and rapidly progressive cause of neonatal distress, cultures of specimens of blood, urine and cerebrospinal fluid should be done and ampicillin sodium (50 to 100 mg per kg intravenously) and gentamicin sulfate (2 to 2.5 mg per kg intramuscularly) should be promptly administered to any distressed infant in whom bacterial infection cannot be confidently excluded. Poor tone and respiratory effort in a newly delivered infant due to maternal narcotic use (either illicit or for obstetric analgesia) will rapidly improve following admin-

istration of naloxone hydrochloride (0.005 to 0.01 mg per kg or 5 to 10 μg per kg given intramuscularly). These infants should be monitored for several hours to ensure that recurrent respiratory depression does not occur.

Summary

We have reviewed the pharmacology of cardiopulmonary intensive care with particular attention to the special considerations required by the unique physiology of a newborn infant. After initial stabilization, as described in Part I of this review, drug therapy may be necessary to improve cardiac output, redistribute the circulation, alter pulmonary function or treat an underlying condition. Cardiac output may be improved by administering drugs that improve myocardial function or that reduce afterload. Agents that redistribute the circulation promote or modify the changes in the circulation that normally follow birth, as the infant makes the transition from the fetal to neonatal pattern of circulation. These drugs reduce pulmonary vascular resistance or cause the ductus arteriosus to remain patent or to close. Although there are numerous conditions that may require additional therapy, treatment of bacterial infection and narcotic intoxication should always be considered for any distressed infant. Despite skillful intensive care consistent with these recommendations, mortality and morbidity remain substantial among infants who require such care. As ongoing research provides new insights into neonatal physiology and resuscitation pharmacology, these guidelines will require modification to allow further improvement in the prognosis of a critically ill neonate.

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Lung Cancer—Current Concepts and Controversies

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The recent literature contains a variety of controversial management alternatives for patients with pulmonary malignancy that affect all aspects of the lung cancer problem. Revisions in the classification system have been advanced in which the prognostic implications of specific ultrastructural and histochemical information are acknowledged. Computed tomography and, to a lesser extent, nuclide scanning have revolutionized the staging process, but limitations in these procedures are emerging. Improved survival following aggressive surgical treatment has challenged the adequacy of the standard staging system. The palliative role of radiotherapy is becoming more widely appreciated. Results of immunotherapy are equivocal and gains from chemotherapy are modest. Combinations of treatment modalities will require further documentation before they can be recommended with confidence.

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Statistics continue to show that the lung cancer epidemic remains unchecked.[1] In 1986 malignant lesions of the lung will kill more than three times as many men as tumors of the colon and lung cancer will surpass breast cancer as the major lethal malignant disease in women by more than 1,000 deaths.[1] Despite an enormous commitment in resources, the medical profession has had minimal effect on the overall lung cancer problem. The annual death rate alone has increased by 5,000 during the past year. The utility of mass screening is questionable.[2] Most attempts at curative resection end in local recurrence or metastasis, and the overall five-year survival remains less than 10%.[3,4] Advances in radiotherapy[5] and chemotherapy[6] have been limited and controversial. Immunotherapy, despite tremendous theoretic potential, still provides negligible clinical benefit. Recent research in tumor biology challenges the adequacy of our traditional classification[7,8] and staging systems[9] and casts doubt on the appropriateness of the conclusions on which they were based.

It should come as no surprise that controversy exists in the management of individual patients with lung cancer. This lack of consensus is not only found among surgeons, chemotherapists and radiotherapists, but is also present within each specialty. The purpose of this paper is to highlight controversies found in the current medical literature.

Overview

Classification

The principal histologic classification of lung cancer was formulated by the World Health Organization (WHO) in 1967.[10] In the past, when fewer therapeutic options were available, generalizations of "squamous," "adeno," "small-cell" and "large-cell" carcinoma were sufficient. Currently, however, variations in therapeutic response make an enhancement of the traditional classification system desirable. Tumors that fail to exhibit discernible histologic organization often have ultrastructural or histochemical findings that permit determination of a predominant cell type.[7,8] Other concepts receiving recognition are that individual tumors often contain more than one cell type and that the primary cell type may, in fact, be altered by therapy.[11]

When more extensive techniques are used, most "undifferentiated" cancers are found to contain one or more of the classic cell types. Using such an approach in 100 unselected cases of lung tumor, 21% were found to be adenocarcinoma, 21% were squamous cell but the majority, or 46%, had combinations of glandular and squamous elements. The remaining 12% were neurosecretory or Clara cell tumors.[12] The WHO modified the original small-cell carcinoma classification system to include a combined category wherein small-cell carcinomas coexist with other histologic types.[13] Alternate classification systems for small-cell anaplastic carcinomas based on their relationship to Kulchitsky's cells and carcinoids have been proposed.[14,15]

Ultrastructural and histochemical analyses have also shed light on the tissue of origin of the various lung tumors. Adenocarcinoma and squamous cell cancers appear to arise from the bronchial epithelium. Some authors feel that small-cell carci-

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ABBREVIATIONS USED IN TEXT

AJC = American Joint Committee for Cancer Staging and End-Results Reporting
BCG = bacille Calmette-Guérin
CT = computed tomography
FEV_1 = forced expiratory volume in one second
RTOG = Radiation Therapy Oncology Group
TNM = tumor-node-metastasis
VA = Veterans Administration
WHO = World Health Organization

nomas are also derived from bronchial epithelium,[11] while others maintain that carcinoids and small-cell carcinomas arise from the Kulchitsky cells of the amine precursor uptake and decarboxylase system.[16] Bronchoalveolar carcinomas arise from alveolar rather than bronchial tissues, and although they may form "glandular" patterns, they should not be considered as subsets of adenocarcinoma.[7] Table 1 presents an outline of the traditional classification system.

The clinical implications of tumor inhomogeneity are obvious: as needle aspiration becomes increasingly popular, fundamental treatment decisions are based on the findings of small biopsies or cytology. Compounding this hazard, the intraobserver and interobserver variations in the histologic interpretation of lung tumors is significant.[17-19] Current techniques in histochemistry, electron microscopy and DNA analysis go beyond traditional boundaries to determine the cell of origin, degree of cellular differentiation, chromosomal homogeneity and other qualities that may accurately predict biologic behavior and response to therapy.[7,8,11,14,15,20-24] In the past, histologic categorization of the predominant cell type has provided useful information related to natural history and response to therapy. Generalizations based on stage and major histologic categories may obscure important population attributes and mask therapeutic opportunities. A prudent physician must be aware of the inherent limitations in sampling nonhomogeneous tumors and in a pathologist's ability to apply classification criteria.

Incidence and Prevalence

In 1986 it is predicted that 22% of all malignant disease in men will arise in the lungs and account for 35% of all cancer deaths.[1] Although accounting for only 11% of malignant lesions in women, pulmonary neoplasms will cause 19% of the cancer deaths. About 149,000 new cases of lung cancer will be detected in 1986: 100,000 in men and 49,000 in women. In 1986 estimates are that lung cancer will account for 130,100 deaths: 89,000 in men and 91,000 in women.[1] This represents an increase over the 1985 estimates of 4,500 deaths. The prevalence of lung cancer among smoking men ranges from 5.3 to 8.2 per 1,000 patients,[2,25] with an incidence of 3 per 1,000 patients per year. The relative frequency of the various cell types can be inferred from two large screening projects summarized in Table 2.[2,25,26] Evidence suggests that the incidence of adenocarcinoma may indeed be increasing.[25-28]

Staging

In 1973 the American Joint Committee for Cancer Staging and End-Results Reporting (AJC) published recommendations for a tumor-node-metastasis (TNM) staging system (Figure 1).[29] Although it has demonstrable utility in predicting patient survival, the adequacy of its nodal specifications has been questioned.[9,30] The system does not differentiate macroscopic from microscopic nodal involvement. The distinction between N_1 and N_2 nodes is arbitrary and occasionally difficult. Similar problems are encountered when separating high mediastinal N_2 nodes from low cervical M_1 metastasis. The term "N_2" refers to any mediastinal node whether it is contralateral or potentially resectable ipsilateral. Finally, patients with nodal involvement at different N_2 locations have had resection with varying survival rates.[30-38] In response, the AJC has described a system of 13 nodal stations (Figure 2) and the American Thoracic Society has provided specific anatomic boundaries for their definitions.[8,30]

Further modifications of the staging system, based on survival analysis, have been proposed.[31,32,38-40] In studies, negligible differences have been found in survival between patients with resected T_1N_1 lesions and those with T_2N_1 lesions, and it has been recommended that both T_1N_1 and T_2N_1 lesions be included in a modified stage II category.[31,38,39] Small central lesions distal to the lobar takeoff behave as T_1 lesions regardless of atelectasis or pneumonitis.[31] Important survival variation exists between patients with squamous and those with nonsquamous cancers when patients with stage I cancers were analyzed.[41] Finally, tradition holds that the TNM system fails to stratify survival rates of patients with small-cell carcinoma, and the simpler classification of "limited" and "extensive" disease is sufficient. Differential survivals, however, have been documented based on the standard TNM system.[42-44]

TABLE 1.—*Traditional Classification System for Lung Cancer*

Histologic Classification
Adenocarcinoma
Well differentiated
Poorly differentiated
Squamous cell carcinoma
Well differentiated
Poorly differentiated
Adenosquamous carcinoma
Bronchoalveolar carcinoma
Undifferentiated carcinoma
Large cell
Giant cell variant
Small cell
Oat cell
Intermediate (fusiform and polygonal)
Mixed

TABLE 2.—*Frequency of Histologic Cell Types From Two Large Screening Projects**

Cell Types	*Memorial Sloan-Kettering,† Percent*	*Mayo Clinic‡*	
		Prevalence, Percent	*Incidence, Percent*
Adenocarcinoma	45	27	24
Squamous cell carcinoma . .	33	43	30
Undifferentiated carcinoma			
Small cell	16	13	26
Large cell	6	17	19

*Based on results from 20,000 screened patients.
†From Flehinger et al[25] and Melamed et al.[26]
‡From Woolner et al.[2]

Natural History

Because efficacy is claimed for various treatment modalities, it is important to understand the natural history of the disease. Ethical considerations eliminate "no treatment" categories from most protocols, although comparisons with historical controls can be misleading. Recent reports continue to emphasize the virulent nature of the disease, and, if carefully used, these data can properly serve as benchmarks for future comparisons.

A group from Sweden thoroughly analyzed the entire population of patients diagnosed with lung cancer during the five-year period from 1971 to 1976 (Table 3).[3] The absolute five-year survival was only 7%. From a cohort of 7,500 patients with inoperable lung cancer, a group of 1,068 patients who received supportive care only were separately analyzed.[45] Those with "limited" disease had a 3.8% two-year survival compared with 0.9% of those with "extensive" disease. Of the patients with extensive disease, the survival was directly related to performance status, with asymptomatic patients achieving a 22-week median survival. The distribution by performance held for all cell types, but patients with adenocarcinoma had longer median survivals (13 weeks) than those with squamous cell carcinoma (9.5 weeks).

Lung cancer appears to be more virulent and extensive in patients younger than 40,[46] presenting as stage III disease nine times out of ten.[47,48] In addition, adenocarcinoma developed in almost half of these patients, and a quarter presented with small-cell carcinoma.[47] Women younger than 50 years had poorer survivals than older women or age-matched men. Of 25 young men resected for cure, 60% survived five years, compared with 16% of 31 young women. The young women had a higher incidence of stage III disease and adenocarcinoma[49]; nonsmoking patients with adenocarcinoma were usually women.[3]

Definitions: TNM Classification

Primary Tumor (T)

T_x Tumor proved by the presence of malignant cells in bronchopulmonary secretions but not visualized roentgenographically or bronchoscopically; any tumor that cannot be assessed

T_0 No evidence of primary tumor

T_{is} Carcinoma in situ

T_1 Tumor 3.0 cm or less in greatest diameter, surrounded by lung or visceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronchoscopy

T_2 Tumor more than 3.0 cm in greatest diameter, or a tumor of any size that either invades the visceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilar region. At bronchoscopy, the proximal extent of demonstrable tumor must be within a lobar bronchus or at least 2.0 cm distal to the carina. Any associated atelectasis or obstructive pneumonitis must involve less than an entire lung and there must be no pleural effusion

T_3 Tumor of any size with direct extension into an adjacent structure such as the parietal pleura or the chest wall, the diaphragm or the mediastinum and its contents; a tumor bronchoscopically demonstrable to involve a main bronchus less than 2.0 cm distal to the carina; any tumor associated with atelectasis or obstructive pneumonitis of an entire lung or pleural effusion

Nodal Involvement (N)

N_x Minimum requirements to assess the regional nodes cannot be met

N_0 No evidence of involvement of regional lymph nodes

N_1 Metastasis to lymph nodes in the peribronchial or the ipsilateral hilar region, or both, including direct extension

N_2 Metastasis to lymph nodes in the mediastinum

Distant Metastasis (M)

M_x Minimum requirements to assess the presence of distant metastasis cannot be met

M_0 No evidence of distant metastasis

M_1 Distant metastasis present

Stage Grouping

Occult stage: $T_x\ N_0\ M_0$
Occult carcinoma with bronchopulmonary secretions containing malignant cells but without other evidence of the primary tumor or evidence of metastasis to the regional lymph nodes or distant metastasis

Stage I: $T_{is}\ N_0\ M_0$
Carcinoma in situ
$T_1\ N_0\ M_0$
$T_1\ N_1\ M_0$
$T_2\ N_0\ M_0$
Tumor that can be classified T_1 without any metastasis or with metastasis to the lymph nodes in the peribronchial or ipsilateral hilar region only or a tumor that can be classified T_2 without any metastasis to nodes or distant metastasis
Note: $T_x\ N_1\ M_0$ and $T_0\ N_1\ M_0$ are also theoretically possible, but such a clinical diagnosis would be difficult if not impossible to make. If such a diagnosis is made, it should be included under stage I.

Stage II: $T_2\ N_1\ M_0$
Tumor classified as T_2 with metastasis to the lymph nodes in the peribronchial or ipsilateral hilar region only

Stage III: T_3 with any N or M
N_1 with any T or M
N_2 with any T or M

Any tumor more extensive than T_2, or any tumor with metastasis to the lymph nodes in the mediastinum, or any tumor with distant metastasis.

Figure 1.—Tumor-nodal-metastasis classification system proposed by the American Joint Committee for Cancer Staging and End-Results Reporting. (Reprinted with permission from JB Lippincott and the American Joint Committee on Cancer.[29])

Screening

The documentation of clear survival differences between lung cancer stages has prompted mass screening projects based on sputum cytology and chest radiography. A Swedish registry recently showed that patients with adenocarcinoma who presented with symptoms had a five-year survival of 3.3%. Those patients whose tumors were discovered by incidental examination had a 13.6% five-year survival, and 30% of patients whose cancer was found during a mass screening project survived five years. The survival advantage suggested by screening, however, was not found for cell types other than adenocarcinoma.[3]

Two large screening projects have recently been reported in the United States by the Mayo Clinic, Rochester, Minnesota, Mayo Lung Project (Figure 3)[2] and the Memorial Sloan-Kettering Cancer Center, New York (Figure 4).[26] Both groups found that half of all cancers could be resected, even though the Mayo Lung Project examined their patients more

TABLE 3.—*Survival of All Patients With Diagnosis of Lung Cancer in the County of Uppsala, Sweden, From 1971-1976 (N = 273)**

Diagnosis	*5-Year Survival, Percent*	*Median Survival, Mo*
Overall survival	7.0	5.0
Cancer free†	8.8	
Adenocarcinoma	11.7	6.7
Squamous cell carcinoma	7.5	7.1
Large-cell carcinoma	3.8	3.6
Small-cell carcinoma	0.0	1.5

*From Nou.[3]
†Excludes deaths from noncancer causes.

frequently. Although shortening the screening interval seems to decrease interval presentations, frequent examinations had minimal impact on overall resectability rates. The Mayo Lung Project found a 50% higher prevalence and a 30% higher incidence of lung cancer. Both projects showed that a third of all cancers were squamous, but the Mayo Lung Project diagnosed twice as many undifferentiated tumors and half as many adenocarcinomas.

Sputum cytology was effective in detecting certain squamous carcinomas but had little value in detecting nonsquamous cell tumors. In the Mayo Lung Project, squamous cell cancer accounted for 30% of all incidence cancers and a third of these were radiologically occult—that is, 12% of all incidence cancers. The authors concluded that although chest roentgenography was four times more productive than cytology, the two tests were indeed complementary. The yield from sputum cytology, however, was low, and false-negative reporting did occur. Adding triannual sputum cytology only detected 12 cases of cancer in 5,000 patients over five years. It was suggested that the carcinomas detected by screening sputum cytology are slow growing and tend to remain localized until they become evident on chest x-ray films.[26]

The Memorial Sloan-Kettering authors stated that the usefulness of screening was established by showing increased survival in resected cases and the greater likelihood of resection in cases detected by screening over those presenting with symptoms. This suggestion may have merit, but important factors that rendered the tumors unresectable are not provided. Incidence and prevalence cases are combined. Of the detected group, 81% were treated at Memorial Sloan-Kettering, whereas 87% of the interval cases were not. Did interval cases have the same high incidence of small-cell carcinoma found by the Mayo Lung Project? Did interval patients have the same aggressive attempts at resection they would have received at Memorial Sloan-Kettering? Finally, does the study design automatically select the most aggressive tumors as interval cases?

The question arises as to whether screening is cost effective. By screening 20,000 patients for five years, 484 lung cancers were detected and the resectability rate was 51%. If one assumes that screening doubled the resectability rate, about 125 of these patients had tumors resected because screening was used. If one assumes a 60% five-year survival for resected cases, then screening salvaged 75 patients, or about 1 salvage per 1,500 patients screened per year. If the cost of screening was $150 per patient, then a quarter of a million dollars was required for each patient salvaged using the procedures described.

With such low yields, even in a high-risk group, extending screening to the general public seems to be a dubious undertaking. The crucial question has yet to be answered: Does screening have any significant impact on overall survival, or does it merely segregate populations with differing biologic potentials? Finally, it can be argued that voluntary screening compliance in a group that ignores smoking warnings contradicts logic. It is incongruous to downplay the elimination of tobacco and imply that frequent screening chest films can somehow negate the consequences of smoking.

Clinical Evaluation

The clinical evaluation of patients with known or suspected malignancy is one of the most controversial aspects of the lung cancer problem. Diagnosis and staging, two major aspects of the clinical evaluation, should remain distinct. It must be emphasized that histology and cytology are the only definitive diagnostic techniques; all imaging modalities merely ascribe probabilities. The question of whether a shadow on chest x-ray films is malignant depends on the radiographic appearance in the context of a specific clinical situation. It is unproductive to suggest general "coin lesion" schemes extrapolated from information obtained from specific populations. A diagnostic algorithm devised for Veterans Administration hospitals may not be appropriate for an outpatient clinic in California's San Joaquin Valley. The workup of coin lesions should be tailored to each case.

If a chest film looks suspicious for carcinoma, a minimal clinical evaluation must include a thorough history and physical examination directed at discovering metastatic disease,

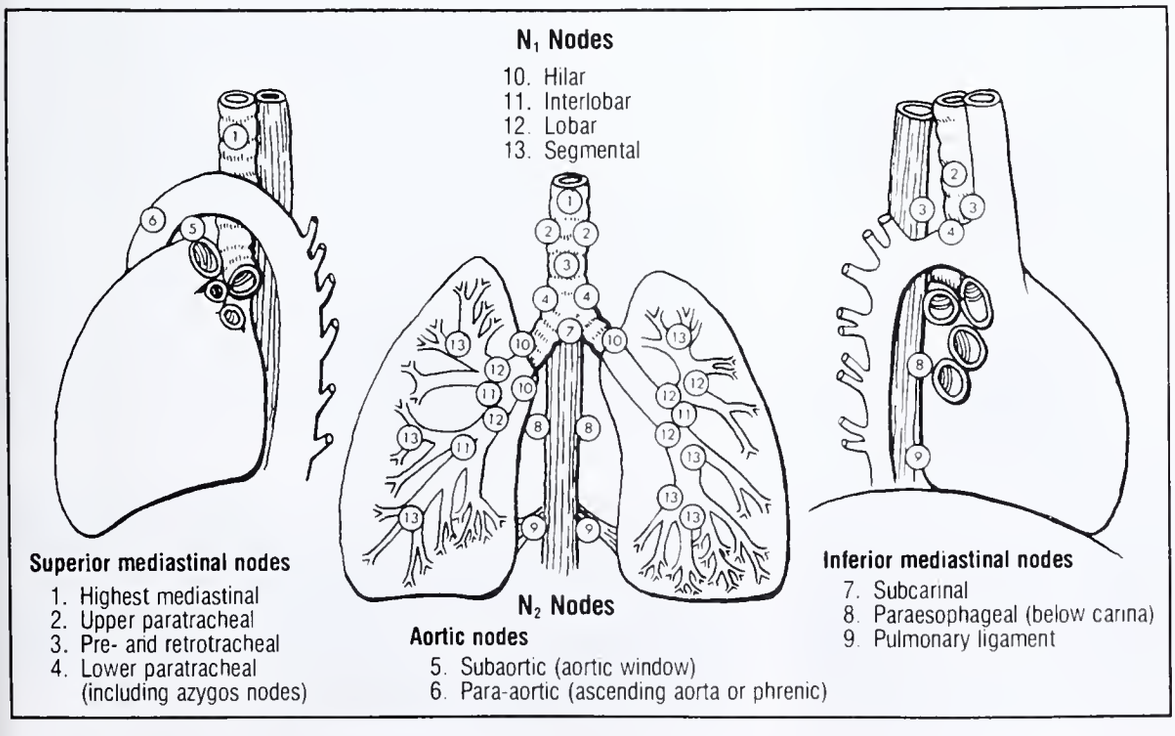

Figure 2.—Definitions of nodal stations used in the tumor-node-metastasis classification system. (Reprinted with permission from JB Lippincott and the American Joint Committee on Cancer.[29])

careful review of current and past chest radiographs, screening laboratory studies with sputum cytology and definitive diagnostic bronchoscopy. Routine nuclide scanning of brain, bone and liver in the face of a completely negative clinical evaluation is generally not warranted. If, however, any question exists after a complete clinical examination, then the threshold for doing these studies should be low. At this point, recommendations for evaluation diverge.

Three procedures have received considerable attention during the past few years: whole-body scans (using bleomycin or gallium), hilar or mediastinal tomography (standard or computed) and invasive staging (mediastinoscopy, mediastinotomy and scalene node biopsy). Each procedure has its own merits and drawbacks.

Diagnostic Radiology

Nuclide Scans

Bleomycin labeled with cobalt 57. The diagnostic capabilities of bleomycin labeled with radioactive cobalt (^{57}Co) were tested in patients with lung cancer.[50] It detected cancer in 96% of the patients and excluded the diagnosis in 87% of patients with benign disease. The sensitivity was decreased in small tumors (less than 2 cm) and adenocarcinoma. Bleomycin ^{57}Co does not differentiate small-cell from non-small-cell carcinoma and it carries a radioactive waste hazard.

Gallium 67. ^{67}Ga is taken up by lung cancer as well as inflammatory and granulomatous diseases. Its sensitivity in detecting carcinoma is estimated to be 90%, and its specificity for nonmalignant disease is 70%.[51] Like bleomycin ^{57}Co it is quite sensitive, but it is less specific as a diagnostic agent. ^{67}Ga does not reliably image lesions smaller than 2 cm. Metastatic lesions may take up the nuclide when the primary is silent.[52]

In addition to its role as a diagnostic modality, ^{67}Ga has been recommended as a staging tool useful in identifying mediastinal involvement and occult metastases. It has been reported to detect silent metastases in 11% of seemingly operable patients.[53] Some authors, however, have not found scanning using ^{67}Ga particularly advantageous.[54,55] Maximizing the value of such scanning requires a level of sophistication (including multiplane tomographic scanners) not present in many general hospitals. Variations in equipment and criteria profoundly affect the utility of the method.[52] Finally, scanning with ^{67}Ga adds little information that cannot be obtained from more widely available tests.[54,55]

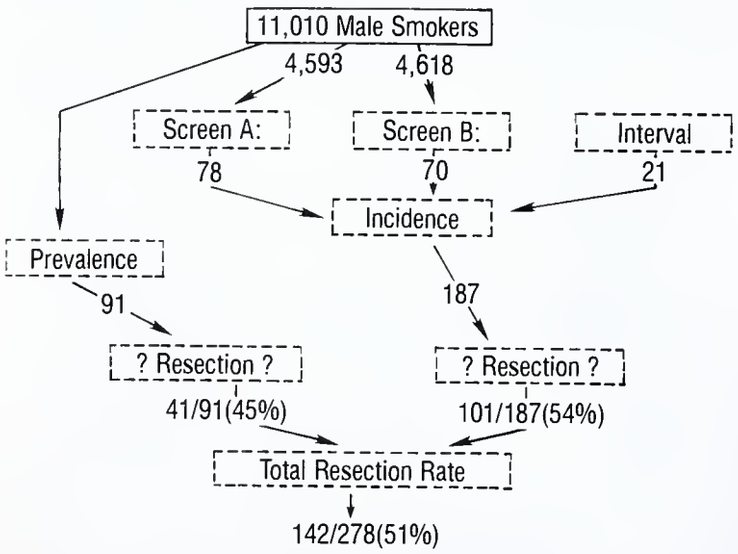

Figure 3.—Flow chart of the Mayo Clinic Lung Project. Screen A: control, with annual chest x-ray; screen B: close surveillance, with chest x-ray and sputum cytology every 4 months. Interval cases, those discovered because of symptoms rather than screening, accounted for 11% of incidence cases; 20% of the close surveillance group were interval cases.

Mediastinal Staging

Computed and Conventional Tomography

A wealth of articles has examined the merits of tomography in mediastinal staging in patients with known or suspected lung cancer.[54-73] Unfortunately, there is wide variation in their results and conclusions. The overall accuracy of either type of tomography ranged from 65% to 95%. Viewed as a whole, there was no clear advantage of computed over conventional tomography in the evaluation of mediastinal or hilar adenopathy, although individual authors promoted the virtues of one process over the other. It is important to understand that two entirely distinct variables are combined: the proficiency of the test and the ability of the radiologist. There were critical differences in these studies that included variations in patient selection, equipment, technique, criteria for positive nodes and indications for contrast material. Some studies were done by committee, while others relied on a single radiologist. A number of the authors corrected their initial interpretations after reviewing the surgical pathology. The criteria for "positive" nodes were arbitrary and varied from any node seen in the mediastinum to only those larger than 2 cm.

In reviewing these data, it is important to remember the significant influence the incidence of positive nodes has on sensitivity, specificity and accuracy.[54,55] It is also important to recognize that some authors included a significant (about 20%) "indeterminant" category for scans that were "too close to call." This has the effect of artificially augmenting the apparent usefulness of the modality.

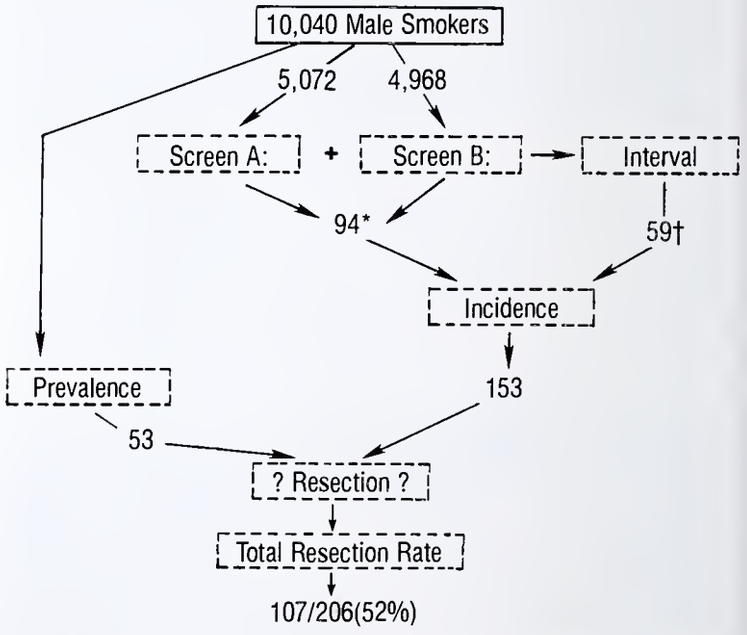

Figure 4.—Flow chart of the Memorial Sloan-Kettering Cancer Center Lung Cancer Screening Project. Screen A: annual chest x-ray, screen B: annual chest x-ray plus sputum cytology every 4 months. The 6-year survival of resected cases was 68%, the 4-year survival for unresected patients was 8%. Interval cases discovered by symptoms rather than screening accounted for 38% of "incidence" cases. (Adapted from Melamed et al.[26]) * = detected case resection rate 63%, † = interval case resection rate 24%

Computed Tomography for Detecting Occult Extrathoracic Metastases

Computed tomography (CT) and nuclide scans have been suggested as methods for detecting covert extrathoracic disease. It is difficult to quantitate the frequency of unrecognized metastasis. Silent distant metastases are most often present in the adrenals, liver, kidneys and brain. They probably occur in at least 20% of patients subjected to surgical treatment.[74,75] The ability of CT to detect these metastases is debatable. One author did CT of the brain, chest and upper abdomen and found asymptomatic metastases in 28.2% of the patients.[71] Another found no abnormal brain CT scans in patients with completely normal findings on clinical examination.[63]

The adrenals are of particular interest because recent articles[70,76-79] show a 10% to 20% incidence of adrenal abnormalities in patients with lung cancer. These rates should be compared with those of the postoperative autopsy series that show 6% to 9% adrenal involvement.[74,75] Review of the CT papers shows that not all patients were surgical candidates. Only one series documented each abnormality histologically.[76] In that series, however, there was the unusual finding that 23% of stage I and II patients had adrenal metastases while only 5% with stages III and IV disease displayed adrenal spread. No explanation is offered of why the incidence of adrenal metastases is four times greater in patients with lower stage disease.

Adrenal enlargements were discovered on abdominal CT in 7% of 60 patients before pulmonary resection. Following the operation, minimal change in the adrenals was noted on follow-up CT.[77] Another study, however, did find disease progression in the adrenals following pulmonary resection.[79] There was no agreement among authors as to what constitutes an adrenal abnormality. The essential question regards the consequences of adrenal enlargement in patients whose tumors are known to secrete adrenocorticotropin-like hormones. It is important to document the natural history of isolated, asymptomatic adrenal abnormalities before adopting a policy that denies surgical resections in any patient population.

The best use of chest tomography is in the staging of patients with lung cancer that is operable and potentially resectable. Negative tomography should preclude invasive staging in most cases. As practiced in most medical facilities, tomography is more useful than gallium scans. It is apparent that different radiologists can be comfortable with either computed or standard tomography as a tool to examine the mediastinum. In this respect, local considerations and individual preference should override isolated literature recommendations. The yield of routine brain, bone and liver nuclide scans in completely asymptomatic patients is low. The natural history of isolated adrenal abnormalities has not been established.

Surgical Staging

Supraclavicular Biopsy

Traditional dogma holds that routine biopsy of nonpalpable supraclavicular nodes should not be practiced. A recent study confirmed this concept for peripheral lesions, but 6 out of 15 patients (40%) with central adenocarcinomas were discovered to have occult supraclavicular metastases. Biopsy of supraclavicular nodes was suggested for central lesions of either unknown or adenocarcinoma cell types.[80]

Mediastinoscopy

The rational use of mediastinoscopy is predicated on a physician's philosophy regarding resectable mediastinal nodal metastases and the confidence placed in noninvasive staging procedures. Mediastinoscopy is reported to have a sensitivity of 79%.[62] Up to 25% of noninvasively staged surgical candidates will be found to harbor positive nodes at mediastinoscopy.[81]

The prognostic significance of mediastinal nodal involvement is controversial because data related to survival following resection are inconclusive.[34,81-83] The controversy is compounded when survival is analyzed by cell type.[34,35,81,82,84] Until the precise natural history of resected N_2 disease—stratified by nodal station, cell type and adjuvant therapy—is defined, it is difficult to place the role of mediastinoscopy into perspective.

Therapeutic Considerations

There is controversy on all aspects of the treatment of patients with lung cancer. Clear-cut reports with reproducible results are the exception. Accepted standards in surgery, radiotherapy, chemotherapy and immunotherapy are lacking. To date, there are only a handful of "axioms" regarding the treatment of patients with lung cancer:

- The treatment of operable, stage I non-small-cell cancers is surgical.
- No adjunctive therapy has shown efficacy for stage I disease.
- Radiation therapy is useful for palliation of symptoms attributable to local disease.
- Intensive chemotherapy has extended the survival of patients with undifferentiated small-cell cancer.

Aside from the above, therapy is largely based on uncontrolled, nonrandomized, retrospective studies that seem to produce more questions than solutions.

Immunotherapy

The illusion still lingers that empyema following pulmonary resection is advantageous because it stimulates the immune system and prevents tumor recurrence. Empyema is a debilitating, often fatal complication whose detrimental effects cannot be rationalized.[41] For those who survive the infection, a handful of reports indicates that patients maintain better local control. An alternate interpretation is that they survived the infection and maintained local control because of some other factor. Reports on the subject are evenly divided as to whether infections are beneficial, irrelevant or detrimental.[85] Recent large series, however, clearly show that infections are associated with a strong negative effect on patient survival.[44,86,87]

Although random bacterial infections are detrimental to humans, specific inoculations may be beneficial. Different strains of bacteria in varying doses and via multiple routes have been investigated. No clear-cut, reproducible clinical improvement has been found.[85] Initial reports indicated a reduction in local recurrences when bacille Calmette-Guérin (BCG) was administered intrapleurally to patients with stage I squamous cell carcinoma.[88,89] Follow-up studies either failed

to confirm the data[90,92] or showed tumor enhancement.[93] Like BCG, *Corynebacterium parvum* has been shown to be associated with a negative effect on survival,[94] while adoptive immunotherapy with leukocyte transfer factor has shown some promise.[95]

Available studies have yet to conclusively prove the efficacy of any immunotherapy protocol, although there may be specific subsets of patients who ultimately benefit. It is equally probable, however, that subsets also exist in whom immunotherapy is harmful. As a corollary, any therapy that impairs the immune system, such as radiation or chemotherapy, may have similar adverse effects. Despite its significant potential, the current place of immunotherapy remains undefined, and its relationship to surgery, chemotherapy and radiotherapy is even more uncertain.

Surgery

Surgical resection is the most effective method of curing lung cancer. For all patients presenting with lung cancer, the following questions should be answered: Is the tumor resectable? If so, can the patient tolerate the proposed resection? Numerous articles have recently addressed the questions of operability, technique, mortality and survival.

Operability

Cardiorespiratory complications account for at least three quarters of postoperative morbidity and mortality.[96,97] Isolated cardiac events account for one of five postoperative deaths, and major morbidity is twice as likely (18% versus 9%) when a history of cardiac disease is present. Patients with cardiopulmonary disease are five times more likely (8.3% versus 1.7%) to suffer postoperative mortality.[98] The annual death rate increased threefold (18.4% versus 6%) when a history of heart disease was present.[41] Significant atherosclerotic heart disease is common in the lung cancer population, and clinical judgment is frequently required in selecting patients. Occasionally there are patients whose coronary disease is so threatening that balloon counterpulsation or even myocardial revascularization may be justified before resection. Specific recommendations regarding ischemic heart disease in determining operability have not been formulated.

The most immediate postoperative threat, however, is not cardiac but pulmonary, and guidelines for determining risk are well established. Methods for predicting postoperative pulmonary status range from purely subjective[75] to highly scientific.[99-101] Although computerized predictions tend to radiate an aura of unchallengeable authority, one must not denigrate the value of a surgeon's impressions gained from physical examination and from observing a patient during exercise.[75]

Operability, however, is more commonly related to spirometric values. Respiratory failure becomes quite probable when the forced expiratory volume in one second (FEV_1) falls between 800 and 1,000 ml (25% to 30% of predicted). In addition, significant cardiac and respiratory complications other than clinically unmistakable respiratory failure are increased when the predicted FEV_1 is less than 50%.[101] There are hazards in predicting the postoperative FEV_1 by simply subtracting the relative amount of anatomic lung to be resected. It should be emphasized that the amount of physiologically functional lung must be subtracted from the preoperative values. Equations have been established that reliably predict the residual FEV_1 based on bronchoscopy or ventilation-perfusion scans.[95-101]

In general, patients who have significant dyspnea, who display hypercapnia or who have an expected postoperative FEV_1 of less than 25% of predicted (800 ml) should not be subjected to resection. Patients who have good exercise tolerance, normal blood gas values and an expected postoperative FEV_1 of greater than 45% (1,500 ml) have a lower probability of respiratory insufficiency, although a significant number of postoperative complications should still be expected.[101] Those patients who have hypoxia, moderate exercise dyspnea or an expected FEV_1 between 25% and 45% of predicted should undergo careful evaluation with ventilation-perfusion scans, an exercise tolerance test or even cardiac catheterization. Finally, in patients expected to undergo lesser procedures, it is extremely important to determine *preoperatively* whether they could tolerate formal pneumonectomy should unforeseen conditions arise.

Procedures

In addition to complete tumor removal, conserving pulmonary tissue is a major surgical objective. Lobectomy is the mainstay of surgical procedures, but the need for pneumonectomy varies between 10% and 55%.[31,75,97,98] Lesser procedures, such as segmentectomy and wedge resection, have been suggested when conserving lung tissue is an overwhelming consideration. Although formal comparisons of wedge resection and lobectomy have not been done, they were both found to produce similar results in two recent retrospective analyses.[31,41]

Other surgical techniques are gaining wider acceptance. These include chest wall resection and bronchoplastic procedures wherein lower lobe bronchi are reimplanted following more proximal resections. Patients requiring chest wall resection face an increased operative risk—2% to 15%—but in the absence of nodal metastases, five-year survivals ranged from 30% to 50%.[102-106] Reconstruction techniques using muscle flaps, grafts and exogenous materials have recently been reviewed.[104] The poor prognosis for patients with nodal metastases makes preoperative staging extremely important. Bronchoplastic procedures carry a low operative mortality—1% to 2%—and five-year survivals range from 20% to 70% depending on nodal status.[107,108] The recent reports on chest wall resections and bronchoplastic procedures fail to show the benefit of preoperative irradiation.

Mortality and Morbidity

No mortality rate can be ascribed to the generic term "thoracotomy." Any mortality rates reflect nonhomogeneous mixes of patients, surgeons and hospital environments. In an analysis of 2,200 patients in The Lung Cancer Study Group, a 3.7% operative mortality was found.[97] In patients younger than 60 years the rate was 1.3%, between 60 and 69 years it was 4.1% and in patients older than 70 years it was 7.1%. Lesser resections carried a 1.4% mortality, lobectomies 2.9% and pneumonectomies 6.2%. An operative mortality rate of 2% was found for all thoracotomies done between 1973 and 1980 at the Memorial Sloan-Kettering Cancer Center.[96] Age and cardiorespiratory status are important factors in predicting operative mortality.[101,106]

Survival

Unfortunately, there is no universally accepted method of reporting survival, and selected techniques have been used to emphasize or validate particular principles. One may draw different conclusions depending on whether operative mortality is included or excluded, whether all deaths or only "cancer deaths" are reported and whether survival was estimated or measured. The quality of follow-up is extremely important. These factors must be considered before a realistic picture of survival and prognoses can be obtained.

Recent reports have been summarized in Table 4. Several factors have a significant impact on survival. In a recent cooperative study, important factors included performance status, cell type, sex, extent of resection, cardiopulmonary status, age, infection or fever, carcinoembryonic antigen, leukocyte count and serum albumin level. None of the standard tests of immune status could be shown to predict survival.[41] In general, operative deaths in good risk patients should be less than 5%. Of patients with $T_1N_0M_0$ tumors, two thirds can be expected to live for five years; if the tumor is $T_2N_0M_0$, this number drops to half. Less than half the patients with $T_1N_1M_0$ or $T_2N_1M_0$ disease will survive five years. Half of the patients with T_3N_0 disease survive five years as compared with a fifth of the patients with resectable N_2 disease. Attaining such results in patients with nodal involvement probably requires curative doses of postoperative irradiation (see "Radiation Therapy" below).

Second Primary or Simultaneous Tumors

Second primary tumors will occur in about 3% of patients postoperatively and, in selected cases, these may also be resectable.[41] Although a 10% to 20% operative mortality has been reported, as many as a third of the patients with resection survived five years.[109,110] Synchronous primary tumors may occur in as many as 7% of the patients. Median survival for patients with stage I disease is reported to be 26 months, but it drops to 11 months for those with stage II and III.[111] Each case must be approached individually, but guarded optimism is justified when the second primary lung cancer is resectable.

Surgical Therapy for Small-Cell Lung Cancer

Although most patients with small-cell lung cancer are initially found with bulky central and metastatic disease, any presentation ranging from isolated peripheral nodules to Pancoast's syndrome[112] has been documented. Until recently, it was generally accepted that the presence of small-cell carcinoma was a contraindication to surgical treatment. Over the past few years, reports have emerged that show the utility of surgical intervention in an adjuvant setting.[11,33,42-44,113] Results are summarized in Table 5.

Recent articles seem to indicate that surgical resection alone may cure some patients with small-cell carcinoma, although patients rarely present with favorable lesions.[42] It also appears that local control is possible using surgical resection, especially when combined with vigorous chemotherapy.[33,43,44,113] There are no studies that show the beneficial effect of an operation plus chemotherapy over chemotherapy alone, or the superiority of surgical treatment over radiotherapy for local control. There are, however, recent retro-

TABLE 4.—*Survival Following Surgical Resection Stratified by TNM Classification System*

Source	Stage	Yearly Survival, Percent 1 Yr	2 Yr	3 Yr	4 Yr	5 Yr
Williams et al, 1981[32]	I*‡	...	...	...	...	56.0
Williams et al, 1981[32]	I*‡§	...	84.0	...	...	69.0
Gail et al, 1984[41]	I*‡‖	...	78.6	...	...	...
Williams et al, 1981[32]	T_1N_0*‡§	...	...	...	...	80.0
Shields et al, 1980[31]	T_1N_0†‖	92.6	75.7	68.5	58.1	52.5
Shields et al, 1980[31]	T_1–T_2N_0†‖	96.2	84.1	66.5	...	...
Williams et al, 1981[32]	T_2N_0*‡§	...	...	...	...	62.0
Shields et al, 1980[31]	T_2N_0†‖	79.1	64.3	53.6	44.6	40.0
Williams et al, 1981[32]	T_1N_1*‡§	...	...	...	...	52.0
Shields et al, 1980[31]	T_1N_1†‖	84.2	37.6	...	...	...
Martini et al, 1983[38]	T_1N_1*‖	...	...	...	...	56.0
Shields et al, 1980[31]	T_1–T_2N_1†‖	85.0	68.6	...	...	...
Shields et al, 1980[31]	T_2N_1†‖	73.5	50.4	39.8	34.1	...
Martini et al, 1983[38]	T_2N_1*‖	...	...	...	...	48.0
McCaughn et al, 1985[105]	T_3N_0*‖	...	...	...	...	56.0
	T_3N_1–N_2*‖	...	...	...	...	21.0
Mountain, 1985[106]	T_3N_0–N_1*‡‖	...	...	...	...	56.0
	T_3N_2*‡‖	...	...	...	...	26.0
Martini et al, 1981[34]; Martini et al, 1980[35]	N_2*‖	73.0	57.0	48.0	38.0	...
Naruke et al, 1978[83]	N_2‖	...	...	...	...	18.8
McKneally, 1983[46]	N_2‖	...	...	...	...	23.0
Pearson et al, 1982[81]	N_2*‖	56.0	36.0	32.0	30.0	24.0

TNM = tumor-node-metastasis

*Actuarial method
†Life-table method
‡Postoperative deaths excluded
§Non-lung-cancer deaths excluded
‖Adjuvant therapy administered in addition to surgery

TABLE 5.—*Small-Cell Carcinoma—Surgical Results*

Source	Patients, Number	Adjuvant Therapy	Operative Death, Percent	Local Control, Percent	Stage	Survival Median Weeks	Survival 5-Year, Percent
Shore and Paneth, 1980[42]	40	None	15	>50	N_1 and N_2	...	25.0
Shields et al, 1982[43]	132	Chemotherapy	16	...	All	...	29.0
	26	...	...	...	$T_1N_0M_0$	...	59.5
	16	...	...	...	$T_1N_1M_0$	...	31.3
	23	...	...	...	$T_2N_0M_0$	...	27.9
	39	...	...	...	$T_2N_1M_0$	...	10.9
	28	...	...	...	T_3 or N_2	...	3.6
Shepherd et al, 1983[44]	35	Chemotherapy	...	95	All	92.4	24.0
		and radiation	...	...	I	158.0	...
		therapy	...	...	I and II	92.4	...

T = primary tumor, N = nodal metastasis, M = metastasis

spective analyses that indicate surgical resection enhances the treatment of patients with small-cell carcinoma.[33,43,44,113]

Chemotherapy

Non-Small-Cell Carcinoma

Chemotherapy for lung cancer has generally been reserved for patients with metastatic disease. Combination, multidrug protocols predominate, while single-agent studies are largely limited to Phase II trials. Protocols that include cisplatin seem to provide improved response and survival rates, particularly in patients with squamous cell carcinoma.[114,115] It must be emphasized, however, that all protocols are experimental, and no regimen for unresectable cancers has gained wide acceptance. Results indicate that a clear response to chemotherapy is associated with prolongation of an otherwise limited survival. In general, patients who are candidates for chemotherapy as a group survive about six months. If patients do not show a response, they live about four months; if they respond, their survival is about one year.[114]

As chemotherapy becomes more intense, increasing toxicity tends to negate any therapeutic gains. Although "responders" survive longer than "nonresponders," the question persists as to whether the drugs function as actual therapeutic modalities or merely as selection agents. The variability of the disease, especially with regard to performance status, must be fully appreciated when analyzing treatment results. Significantly enhanced survival awaits precise patient selection through the ability to predict individual responses to specific chemotherapeutic agents.

Small-Cell Carcinoma

Several excellent reviews summarize the current status of small-cell lung cancer management.* The results of chemotherapy can be viewed on either relative or absolute scales: one is encouraging, the other dismal. On the positive side, aggressive multidrug chemotherapy has quadrupled median survival. The quadrupled median survival, however, is still only 12 months. The first confirmed five-year chemotherapy and irradiation cure was, in fact, not reported until 1984![118] The price for this accomplishment has been high in terms of morbidity and mortality.[119] Serious complications of leukopenia, infection, esophagitis, pneumonitis, pulmonary fibrosis, cardiac toxicity, secondary malignancy and neurologic and psychological damage are common.[6,119,120] These problems are often amplified by the addition of irradiation.[121]

State-of-the-art chemotherapy provides the following results for patients with limited and extensive-stage cancer, respectively: complete response rate, 50% and 25%; median survival, 14 and 7 months; three-year survival, 20% and 0%. Chemotherapy alone is associated with a local failure rate of 50%. This can be reduced to 25% with adjuvant radiotherapy[11] or surgical resection.[33,44,113] Further studies are needed before any combination of treatment modalities is established.

Radiotherapy

There is no place in the management of patients with lung cancer wherein the specific details of treatment are so imprecisely defined as with radiation therapy. It is extremely difficult to make meaningful generalizations because the recent literature abounds with uncontrolled variables and conflicting results. Impressions have been formed from small, uncontrolled or retrospective studies involving nonhomogeneous patient populations. Stratification for cell type, stage, performance status, previous therapy and immunologic level is often lacking. There is disagreement regarding radiation type (external, internal, particle, photon), dose (3,000 to 6,000-plus rads), schedule (short, split, standard or long course) and intent (curative, palliative, adjunctive or prophylactic). Conclusions are derived from trends and suggestions, while end points of tumor response and local control have replaced "survival" and "quality of life." Accordingly, reviews of radiotherapy published since 1980 have ranged from glowing[122-125] to gloomy.[5,126,127] There are several categories in which these divergent opinions can be examined: radiation therapy as an alternative in resectable patients, radiation therapy for cure in patients with localized nonresectable disease, radiation therapy in an adjuvant setting, radiation therapy for prophylaxis and radiation therapy for palliation.

Radiation Therapy for Cure

Recent reports continue to show the inferiority of external radiation therapy when compared with surgical treatment.[127] It has been well shown, however, that external irradiation can sterilize smaller tumors in 25% to 50% of patients. These results might tempt one to suggest that radical radiation therapy is the treatment of choice in patients whose pulmonary function precludes operation. The restrictions of pulmonary function, however, are similar for both radiation and surgical therapies,[124] and irradiation remains a poor choice compared with surgical resection.[127]

Radiation Therapy as a Surgical Adjuvant

Preoperative. Preoperative irradiation has been largely abandoned because benefits that might be gained in tumor "downstaging" are lost in postoperative mortality and morbidity. There is one area, however, in which preoperative irradiation has been widely practiced: chest wall invasion, particularly in patients who have pulmonary apical tumors with Pancoast's syndrome. In recent studies, preoperative and postoperative radiation therapy was used in an uncontrolled fashion.[102,103,128] Although the studies failed to show a significant increase in survival, results did suggest improved operability and local control. Survival was conspicuously related to mediastinal involvement.

Patients with T_3 apical tumors, classic Pancoast's syndrome and negative mediastinal nodes are candidates for preoperative irradiation (3,000 rads), followed by radical en bloc resection. It should be remembered that this approach is based on results of uncontrolled, retrospective studies of selected patients. If mediastinal nodes are involved, or if diaphragmatic or vocal cord paralysis exists, or if other indications of mediastinal extension are present, complete surgical resection is unlikely. Reasonable palliation can be expected from definitive external irradiation.[129,130] Incomplete resection combined with "brachytherapy" (intraoperative implantation of permanent or temporary radiation sources) also provided meaningful palliation in such cases.[123,131]

Postoperative. Postoperative irradiation can be analyzed in patients in whom residual tumor is unlikely (N_0 and clear

*References 11, 33, 43, 44, 113, 116, 117.

margins) and those in whom residual tumor is probable (N_1, N_2, positive margins). Numerous studies have failed to show that prophylactic radiation therapy following "curative" resection in patients with negative nodes offers any advantage. There are indications that this prophylaxis may, in fact, be harmful.[132] The evidence for postoperative irradiation in patients with nodal involvement is much more controversial and several authors have addressed the issue.

In retrospective nonrandomized studies, postoperative radiation therapy appears to improve survival, particularly in patients with squamous cell carcinoma.[36,82,133] A fourfold increase (10% to 40%) in three-year survival was recorded when patients with squamous cell carcinoma and N_1 or N_2 disease received postoperative irradiation.[133] In other nonrandomized, uncontrolled reviews, improvements found with postoperative irradiation were only significant for patients with adenocarcinoma.[34,35] Studies, therefore, exist that suggest that postoperative radiation therapy in patients with squamous cell carcinoma is harmful,[132] equivocal[34,35,134] and helpful.[36,82,133] There is no explanation for the apparent divergent response to radiotherapy, and caution should be exercised in recommending or withholding radiation therapy based on cell type.

Adjuvant Prophylactic Cranial Irradiation

Unrecognized brain metastases have plagued patients with small-cell cancer and adenocarcinoma. Prophylactic cranial irradiation has been advanced as a solution to this problem. The Veterans Administration (VA) Lung Group examined this question by stratifying a thoracic irradiation protocol into patients who received prophylactic cranial irradiation and those who did not.[135] Prophylactic cranial irradiation was associated with a statistically insignificant reduction in the rate of brain metastases in patients with small-cell carcinoma, from 33% to 22%. Patients with adenocarcinoma, however, showed a dramatic drop in the rate of brain metastases from 29% to 0% with prophylactic cranial irradiation. No survival advantage, however, was shown for those who received the cranial irradiation. Other studies have also failed to document that prophylactic cranial irradiation increased survival.[11] One report found that it was associated with an increase in brain metastases.[44] It should be remembered that in the few patients in whom brain metastases represent the only known disease, adequate palliation of symptomatic cranial deposits can usually be achieved. Because brain relapse may occur in 20% of patients despite prophylactic irradiation, it seems appropriate to limit this treatment to that subset of patients who have already shown a complete tumor response.

Radiotherapy as an Adjuvant for 'Positive Margins'

A report from a pathologist of "microscopic disease at the bronchial margin" has prompted responses ranging from expectant observation to reoperation or radiation therapy. Reports can be found of long-term survivals in patients with untreated positive bronchial and vascular margins.[75,136] Increased survival has not been shown in patients with microscopically positive bronchial mucosal margins when treated with postoperative irradiation.[136] If the margin, however, contained malignant lymphatic permeation, peribronchial tumor or recurrent disease rather than just mucosal invasion, survival was uniformly poor. There has been no direct investigation of re-resection versus radiation therapy versus expectant observation. The presence of a positive mucosal margin, however, is one category of residual disease that does not appear to mandate additional therapy. Until definite recommendations evolve for the other categories, persistent efforts to eradicate residual or recurrent disease seem justified.

Although a specific survey is not available, a review of the recent literature would support the proposition that "standard therapy" for patients with a strong probability of residual disease includes the delivery of postoperative "curative intent irradiation"—more than 4,000 rads—to the mediastinum. There are, however, no randomized, prospective studies that clearly and reproducibly provide justification for this approach. Irradiation carries the associated morbidity of temporary esophagitis, pneumonitis, pulmonary fibrosis, myelosuppression and immunosuppression.[137] Although

TABLE 6.—*Unresectable Lung Cancer—Radiotherapy Results of Several Protocols*

Source	Patients, Number	Protocol*	Cell Type	Median Survival, Wk					Response Rate, Percent		
				Non	Partial	Complete	Comb	All	Partial	Complete	Comb
Petrovich et al, 1981[138]	343	1A,1B	All	31	47	64	50	38	34	4	38
			Squamous	...	...	...	...	56	...	...	52
			Non-squamous	...	...	...	...	32	...	...	...
Perez et al, 1980[141]	378	All	All	31	44	69	...	...	...	...	...
	261	All	Squamous	...	...	...	...	41	...	...	50
	57	All	Adeno	...	...	...	...	39	...	...	65
	51	All	LC	...	...	...	...	52	...	...	75
	100	2A	All	...	...	...	...	...	...	8	46
	101	2B	All	...	...	...	...	...	...	...	51
	92	2C	All	...	...	...	...	...	...	24	66
	85	2D	All	...	...	...	...	...	...	...	61
Salazar et al, 1984[144]	49	3	All	...	...	...	...	...	...	27	...
	20	3	Squamous	...	...	...	...	...	...	...	75
	20	3	Adeno	...	...	...	...	...	...	...	45
	9	3	Undif	...	...	...	...	...	...	...	100

Adeno = adenocarcinoma, Comb = complete and partial response combined, LC = large-cell carcinoma, Non = nonresponder, Undif = undifferentiated carcinoma

*Protocols: 1A = 5,000 rads in 25 fractions in 5 weeks;1B = 4,200 rads in 15 fractions in 3 weeks; 2A = 2,000 rads in 5 fractions in 1 week, 2-week pause, then 2,000 rads in 5 fractions in 1 week; 2B = 4,000 rads in 20 fractions in 4 weeks; 2C = 5,000 rads in 25 fractions in 5 weeks; 2D = 6,000 rads in 30 fractions in 6 weeks; 3 = 5,000 to 6,000 rads once a week.

some reports seem to suggest a number of benefits, others urge increased caution until specific criteria are conclusively established.

Radiation Therapy for Unresectable Tumors

The problem of radiation therapy for unresectable tumors is complex and confusing. This is most evident when reviewing the results published in several recent trials (Table 6). The VA Lung Group concluded that median survival and response rates were significantly better for patients with squamous cell carcinoma. Performance status and weight loss were also found to be important predictors of survival.[135,138,139] The Radiation Therapy Oncology Group (RTOG) randomly assigned patients to split-dose and increasing continuous dose protocols.[140,141] The complete response rate was found to be higher in the continuous-dose group and the two-year survival doubled when the patients received at least 5,000 rads. Local control was directly related to radiation dose.

Interesting differences are found when the results of the VA Lung Group and the RTOG are compared. This is particularly the case when the median survivals are stratified for response rate and cell type. Similarities were found for patients with squamous carcinoma, but patients with adenocarcinoma and large-cell carcinoma responded better in the RTOG protocols. The RTOG and VA Lung Group both showed that squamous cell cancers recurred locally about twice as often as glandular carcinomas (20% versus 40%). Higher radiation doses seem to be required to control squamous cell carcinomas.[141]

These reports address the question of therapeutic efficacy in a number of ways: response rate, site of relapse, disease-free interval and median and yearly survivals. Generalizations that appear to be true in selected response categories may be ambiguous or conflicting when viewed in relation to others. For example, the group most likely to have relapse in the thorax is least likely to have overall evidence of clinical failure; the trend toward local control is offset by an increase in distant metastases. Specific subpopulations and end results can be selectively emphasized to create the impression that one dose or fractionation is superior to another.

The major question, however, remains: does radiation therapy produce any tangible benefit to patients with unresectable lung cancer? The earlier Oxford trials allowed physicians to choose whether their patients were to be placed in "observation" or "mandatory treatment" groups. Although this selection may have introduced significant bias, it was nonetheless concluded in these studies that radiotherapy may well be detrimental and that, except for palliating the specific symptoms of pain, hemoptysis and superior vena cava obstruction, no therapy was indicated.[142-144] Many studies find that "responders" live longer than "nonresponders." Whether the radiation therapy itself is beneficial, however, or whether the stress merely selects the most durable patients has not been established.

Combined Therapy

In the future, most patients with lung cancer will undoubtedly receive combinations of surgical resection, irradiation, immunotherapy and chemotherapy. Treatment failure patterns in patients with limited disease suggest that adjuvant systemic therapy is desirable.[40,41] Many authors have found that adjuvant radiotherapy enhances local control in patients with mediastinal nodes.[34,35,38,82,123] Others have shown incremental survival advantages when chemotherapy was added to surgical and radiation therapies in advanced tumors.[39,95,145-148] Combined therapy is very attractive on theoretic grounds, but the eventual role of combined therapy awaits further definition. Increased response rates can be expected when individual modalities are extended to toxic levels, but concomitant increases in morbidity and mortality currently offset any gains.

Conclusions

Many difficulties arise when managing patients with lung cancer. Until more effective treatment modalities displace our present techniques, improved survival remains predicated on more precisely allocating available therapies. Eliminating "nonresponders" from radiation, immunotherapeutic and chemotherapeutic protocols must have the same priority as eliminating "unnecessary thoracotomies" from surgical practice. A literature review such as this emphasizes the complexity and variability of the overall tumor-host interaction. Failure to adjust for this variability when analyzing the efficacy of treatment modalities may account for the wide spectrum of results and recommendations. The large number of subjects required to stratify and compensate for the inherent variance of the disease limits from the outset investigative attempts by single institutions. Comprehensive, cooperative trials using our most sophisticated analytic tools offer the best hope of securing a positive legacy for future patients and physicians.

Lung cancer will remain a primary health menace for the foreseeable future. Efforts at control are thwarted by our limited ability to treat established disease and our failure to curtail environmental pollution and cigarette consumption. Our therapeutic limitations are placed into ironic perspective by the fact that lung cancer is largely a preventable, self-inflicted disease.

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Specialty Conference

Diagnostic Immunopathology

Moderator and Discussant
PASQUALE A. CANCILLA, MD

Discussants
ALISTAIR J. COCHRAN, MD; FARAMARZ NAEIM, MD, *and* JONATHAN W. SAID, MD

An edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. The Director of Conferences is William M. Partridge, MD, Professor of Medicine.

The application of immunologic techniques to tissue sections has added a new dimension to the investigation and classification of various processes. Virtually every section of diagnostic pathology has been enhanced by using specific monoclonal antibodies or polyclonal antiserum. Neoplasms formerly diagnosed as poorly differentiated or anaplastic may be precisely identified as to their origin through the use of specific membrane or cytoplasmic markers. Other cellular products, including viruses, hormones, enzymes or highly specific proteins, are also available to study neoplastic and nonneoplastic processes. New and more specific reagents are regularly becoming available for the diagnostic repertoire of pathologists. We present some of the principles of diagnostic immunopathology to show the scope and importance of the techniques.

(Cancilla PA, Cochran AJ, Naeim F, et al: Diagnostic immunopathology [Specialty Conference]. West J Med 1986 Jul; 145:65-73)

PASQUALE A. CANCILLA, MD:* The application of immunologic techniques to tissue sections has now gained wide acceptance as an important addition to the diagnostic armament of pathologists. These techniques, which use monoclonal or polyclonal antibodies to specific determinants of the cell or its extracellular environs, have specific features that facilitate accurate diagnosis or classification of disease processes.[1,2]

Diagnostic immunochemistry originated in the 1940s with the conjugation of fluorescent tracers such as fluorescein isothiocyanate directly to an antibody (Figure 1).[3] Inducing this reaction between an antigen and its conjugated antibody is referred to as the *direct method.* In the *indirect method,* the antigen and its antibody react before the conjugated antibody is introduced, which in this case is derived from another species and is directed against the globulin moiety of the initial specific antibody. These techniques were used to diagnose renal diseases and various immune disorders of the skin and to show certain cellular products, such as viruses, hormones, enzymes or proteins. The technique required frozen sections of unfixed or partially fixed tissue to show the putative antigen in the tissue, and this seriously limited the applicability of these procedures for diagnosis. A pathologist usually works with fixed, rather than fresh, tissue and paraffin-embedded, rather than frozen, material.[4] Also, the frozen section technique did not result in a permanent section or a durable stain; it required the use of a fluorescence microscope for the examination, and it had less image resolution than tissue processed in the conventional way, thus further limiting its usefulness.

Some of these problems have been overcome by the development of enzyme-conjugated antibody procedures that use fixed, paraffin-embedded tissue sections and correlate directly with standard stains in the same or adjacent sections. These procedures may be amplified by increasing the time of incubation or the amount of enzyme bound to the tracer. They also yield a permanent slide for review and can be treated to control or eliminate various artifacts.[1] Thus, the peroxidase-antiperoxidase and the avidin-biotin conjugation techniques are now in regular use in diagnostic immunopathology (Figure 1).

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
GFAP = glial fibrillary acidic protein
Ig = immunoglobulin
kd = kilodalton

Coincident with the development of these methods to show antigens in tissue sections has been the production and the ready availability of a wealth of specific monoclonal antibodies or useful polyclonal antiserum of diagnostic importance. These techniques are now used in every specialty area of pathology because of their specificity, sensitivity, reproducibility, easy application, availability and importance. Cost benefits can be linked directly to the greater diagnostic accuracy that reduces costly clinical investigations resulting from less specific diagnoses.

The entire field of diagnostic immunopathology cannot be covered in this conference. We have, therefore, selected four topics to show the power and importance of the techniques and to direct interested readers to other sources for more complete reviews of the subject.

Immunodiagnostic Approaches to Neoplasms of the Nervous System

Primary or metastatic neoplasms of the central nervous system constitute an important group of human neoplasms that include the gliomas (astrocytomas, oligodendrogliomas, ependymomas), ganglion cell tumors (gangliogliomas, ganglioneuroblastomas), medulloblastomas, meningiomas, schwannomas, hemangioblastomas, sarcomas, lymphomas and epithelial and nonepithelial metastases. Given such a heterogeneous group of neoplasms, the ready availability of monoclonal antibodies and polyclonal antisera, the frequency of origin of some of these tumor types from the neuroectoderm and the variability in the degree of differentiation of some of these neoplasms, it is not surprising that immunodiagnostic techniques have been applied extensively to assist in the diagnosis and classification of the less differentiated or equivocal neoplasms.[5]

Table 1 lists the common immunologic reagents used to assist pathologists in diagnosing and classifying neoplasms of the nervous system. The list is not comprehensive as several other available immunologic markers are used in special circumstances.[5,6] Also, the battery of markers available for metastases, lymphomas and melanocytic neoplasms is not included as some of them will be presented in detail in other parts of this conference.

The antiserum for glial fibrillary acidic protein (GFAP) is the most useful and most frequently applied reagent.[7-9] It is not a specific marker for astrocytic neoplasms in that it also reacts with nonneoplastic astrocytes, some ependymomas and some choroid plexus papillomas.[5] Because astrocytomas are the most frequent neoplasm of the nervous system and because GFAP has only been shown in cells of neuroectodermal origin, it is the benchmark for all other stains.

The origin and nature of GFAP-positive cells in other nervous system neoplasms is debatable.[5] For instance, scattered GFAP-positive cells have been found in hemangioblastomas, medulloblastomas and pineal blastomas.[5] In some instances, the presence of GFAP-positive cells has been interpreted as evidence of glial differentiation of the more primitive neoplastic cells, whereas in other instances their presence has been attributed to the phagocytosis by neoplastic cells of GFAP released by reactive astrocytes associated with the neoplasm.

S-100 protein is a useful marker for several neoplasms of central or peripheral nervous system origin.[5,9] Its range of application will be presented later in this conference, but it is important to describe some of its properties now because it is frequently used to identify, or investigate, neoplasms of the nervous system of equivocal origin or in which a neoplasm of more than one cell type may be present.[10] In the former instance, astrocytomas and schwannomas react with this reagent, and it is helpful to be able to substantiate an impression that one is dealing with a neoplasm of one or the other type. In mixed neoplasms, such as glial sarcomas, the glia may be separated from the sarcomatous elements by this reagent.

Neuron-specific enolase enjoyed brief popularity as a marker for nonneoplastic and neoplastic ganglion cells and for identifying various neoplasms referred to as either the amine precursor uptake and decarboxylation tumors or neuroendocrine tumors of various tissues.[11,12] Because the reagent has been shown to be reactive with various nonneuroendo-

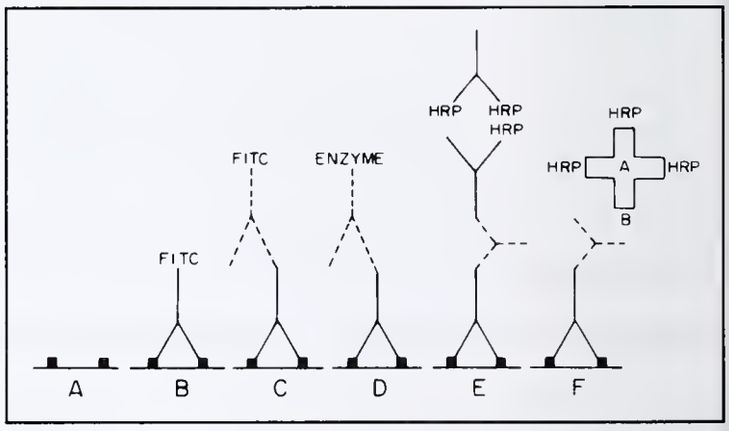

Figure 1.—The immunohistochemical demonstration of a surface antigen. **A,** Surface antigen, unreacted; **B,** specific antibody bound to antigen; **C** and **D,** direct antibody method with fluorescein isothiocyanate (FITC) or enzyme; **E,** indirect method with peroxidase-antiperoxidase; **F,** indirect method with avidin-biotin conjugation. HRP = horseradish peroxidase

TABLE 1.—*Immunohistochemical Markers for Nervous System Neoplasms**

Antiserum	*Diagnostic Application*
Glial fibrillary acidic protein	Reactive astrocytes Astrocytomas Some choroid plexus papillomas
S-100 protein	Reactive astrocytes Astrocytomas Schwannomas Some meningiomas
Neuron-specific enolase	Neurons Gangliomas and ganglion cell neoplasms Amine decarboxylation tumors Some medulloblastomas
Factor VIII-von Willebrand	Normal, reactive and neoplastic endothelium
Desmin, myosin	Normal and neoplastic smooth and striated muscle

*These are some of the commonly applied immunohistochemical markers. Markers useful in the investigation of metastasis are not included.

crine neoplasms, its presence in a neoplasm requires careful interpretation.[11,13]

The factor VIII-Von Willebrand-related antigen is a useful marker for endothelium and megakaryocytes. For endothelium, it may show normal and hyperplastic endothelium associated with neoplasms, such as astrocytomas. It may also stain neoplastic cells of endothelial origin in glial sarcomas or in angiosarcomas of peripheral tissue.[14-16]

Desmin and myosin are components of smooth and skeletal muscle, and antiserum to these proteins may be used to identify neoplasms of smooth or striated muscle.[17]

Figure 2 shows how several of the antiserums described above may be valuable in definitively classifying a neoplasm. The neoplasm was a solitary mass lesion from the right cerebral hemisphere of a 27-year-old woman. The routine hematoxylin and eosin stain (Figure 2-A) showed a cellular neoplasm in brain tissue composed of spindle cells and scattered larger cells. The neoplasm could not be classified further; a broad differential diagnosis included glial sarcoma, meningeal sarcoma, rhabdomyosarcoma, leiomyosarcoma or angiosarcoma. The GFAP stain (Figure 2-B) showed scattered GFAP-positive cells that were interpreted as reactive and not neoplastic astrocytes. The S-100 protein gave a similar staining pattern, confirming the nonglial nature of the neoplasm. The myosin antiserum (Figure 2-C) stained only the large cells, but its specificity led to the conclusion that the neoplasm was a rhabdomyosarcoma. This diagnosis was further substantiated through the use of the antiserum for desmin, which stained the large cells and the spindle cells (Figure 2-D).

S-100 Protein as a Marker for Melanocytic and Other Tumors

ALISTAIR J. COCHRAN, MD:* The diagnosis of malignant melanoma presents few problems when the tumor or the skin surrounding it contains abundant melanin pigment. This is the case at the clinical and microscopic levels. Problems arise in those primary and metastatic melanomas in which melanogenesis is switched off. At the microscopic level, the situation becomes especially difficult when the cells adopt unusual cytologic morphology and resemble nonmelanocytic lesions or benign melanocytic lesions.[18] In the past, attempts to categorize such debatable tumors as melanoma and separate them from other tumors that might resemble melanoma, such as large-celled lymphoma, renal carcinoma and spindle cell carcinomas or sarcomas, relied heavily on histochemistry using the relatively unique enzyme systems involved in the synthesis of melanin and on the ultrastructural demonstration of melanosomes, organelles unique to melanocytes and cells derived from them.[19] The problem with these approaches is that both require fresh tissue for optimal results and, in most cases, by the time it is realized that there is a problem, fresh tissue is no longer available.

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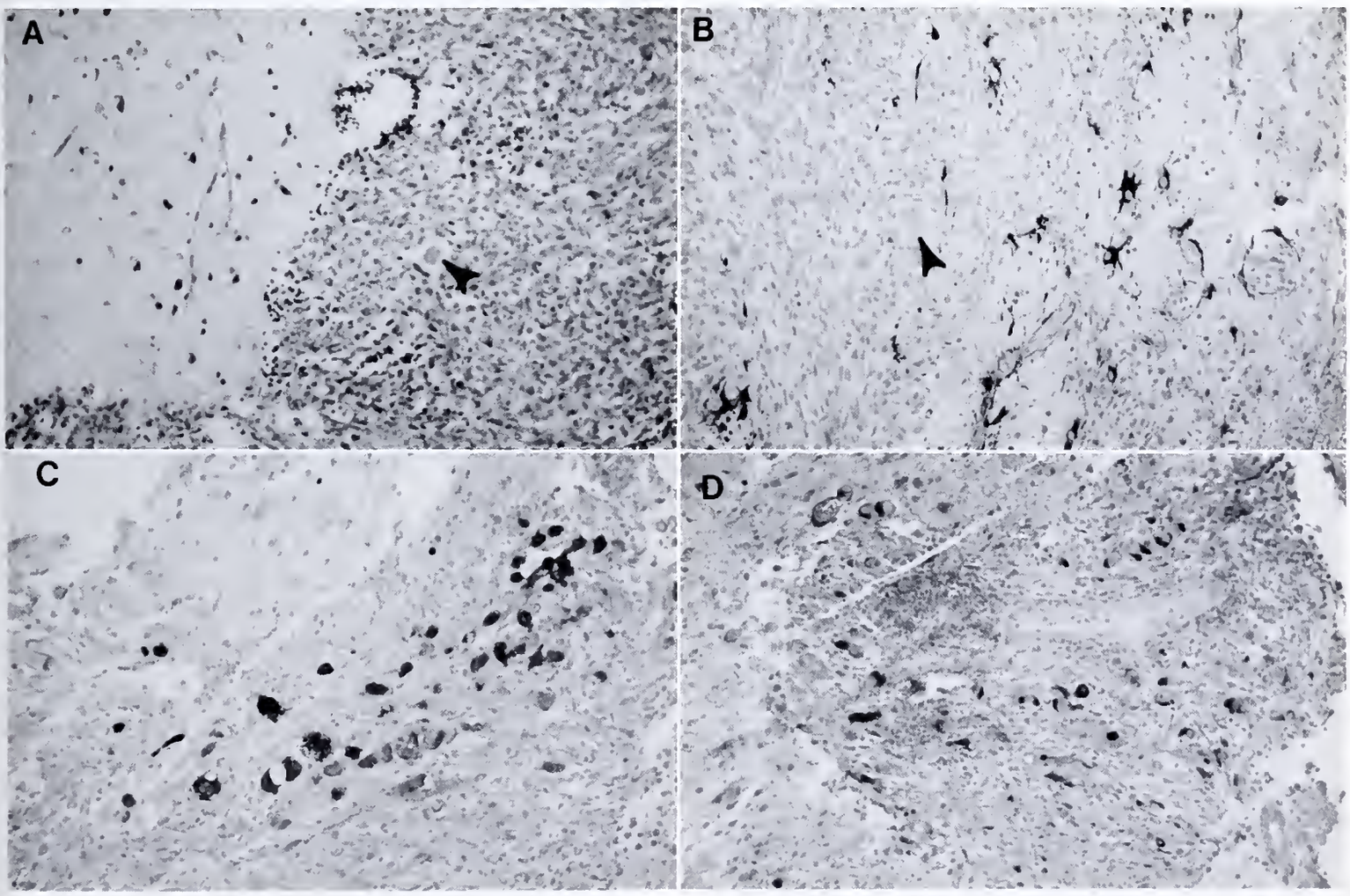

Figure 2.—Histologic and histochemical demonstration of a cerebral neoplasm. **A,** Small spindle cells and scattered large cells **(arrow)** make up the neoplasm (hematoxylin and eosin stain). **B,** This glial fibrillary acidic protein stain shows reactive astrocytes. Neoplastic cells are unstained. **C,** This myosin stain reacts only in the large and small cells. **D,** Large cells and spindle cells are shown with antiserum for desmin.

Recently we and others have used the detection of S-100 protein as an additional means of identifying tumors as melanocytic.[20-28] S-100 protein was extracted from bovine brain by Moore.[29] It is an acidic protein named for its solubility in saturated ammonium sulfate. S-100 protein has a molecular weight of 21,000 daltons and is present in the nervous system of many different mammals, its concentration increasing with age. It is found mainly in cell cytoplasm, although there are reports that some S-100 protein is present in a membrane-bound form. The initial studies found S-100 protein in glial cells, Schwann cells, satellite cells of ganglia and debatably in certain neurons.[30] More recently it has been found in the satellite cells of the adenohypophysis, the satellite cells of the adrenal medulla, type II cells of the carotid body, the interstitial cells of the pineal and the Müller cells of the retina. Until recently, S-100 protein was regarded as a neuroprotein, having been found only in cells associated with the nervous system, but more recent studies show it in extraneural tissues. The biochemistry and distribution of S-100 protein are reviewed in detail in a recent article.[30]

In 1980 Gaynor and associates reported that S-100 protein was detectable in cultured malignant melanoma cells, cells derived from melanocytes that in turn had their embryologic origin in the neural crest.[20] In the following year, Cocchia and co-workers found S-100 protein in normal melanocytes.[31] These findings, per se, did not undermine the view that S-100 protein was closely related to the neural system. Since 1981, however, an increasing number of investigators have recorded S-100 protein in various nonneural tissues, including chondrocytes, adipocytes, myoepithelial cells, dendritic cells of lymphoid tissues and skin, some macrophages and possibly even some classes of T lymphocytes.[30] Because these cells are not neural and are mostly not derived embryologically from neuroectoderm, it seems likely that in these cases the presence of S-100 protein indicates some functional activity shared between this group of (nonneural) cells and neural cells.

In 1981 and 1982 we and others, using immunofluorescence and immunoperoxidase techniques, reported that S-100 protein was detectable in virtually all cutaneous melanomas.[21-24] Since that time, tissue evaluation for S-100 protein has rapidly become part of the routine workup for debatable tumors possibly derived from melanocytes. We have found S-100 protein, in combination with other markers (such as cytokeratins and leukocyte antigens), most useful in identifying tumors of debatable histogenesis, in identifying metastatic deposits in lymph nodes and other viscera, in separating tumor replacement of the lymph node sinuses from sinus histiocytosis and in categorizing spindle cell neoplasms of debatable histogenesis. This usually involves separating spindle cell desmoplastic melanoma from spindle cell squamous carcinoma and spindle cell sarcoma. The S-100 protein approach can also be applied to ocular melanomas.[22,28] Studies of malignant melanoma have been paralleled by examination of various classes of nevocytic nevi. S-100 protein is common to benign and malignant melanocytic tumors and is, therefore, not a marker for malignancy.

A major problem with the use of S-100 protein is that it is not an absolutely specific marker for melanocytic tumors. It can be readily detected in various neural system tumors including gliomas, retinoblastomas with glial differentiation, meningiomas, benign and malignant schwannomas, neurogenic sarcomas, neurofibromas and benign and malignant granular cell tumors. The separation of spindle cell melanoma from schwannomas is a particularly difficult problem. Recent studies have indicated that the S-100 protein molecule is a dimer, consisting of two separate subunits, designated a and b. Melanocytic lesions contain both a and b subunits, whereas the schwannian lesions contain only the b subunit. Separation of these classes of tumors should therefore be possible using antiserum to the relevant subunits.[33,33]

Various nonneural tumors have been found to contain S-100 protein. These include chondromas, chondroblastomas, chondrosarcomas, liposarcomas and the chondroid portions of osteosarcomas. This reactivity would have been predictable on the basis of the known normal tissue reaction pattern of S-100 protein. Less predictable is the observation that occasional breast cancers and pleomorphic adenomas of the salivary glands contain S-100 protein. These are probably tumors in which myoepithelial cells are abundant, and it is this cell that is reactive. In these tumors, a careful consideration of the clinical history and the use of ancillary special stains and immunohistochemical reagents, such as those directed to the cytoskeleton and to milk-fat globulin, may be of assistance in revealing their true identity.

Various histiocytic tumors have been found to contain S-100 protein. These include tumors arising from the dendritic cell system, including benign and malignant histiocytosis X,[34,35] histiocytic medullary reticulosis[36] and Langerhans's cell granulomatosis. Other "histiocytic" tumors, such as sinus histiocytosis with massive lymphadenopathy, may also contain S-100 protein.[37] Separation of these conditions is also facilitated by the use of antibodies to the S-100 protein subunit. Cells derived from the dendritic cell series expressed the $S\text{-}100_b$ subunit, whereas those derived from the more conventional macrophage-histiocyte series expressed the $S\text{-}100_a$ subunit.[38]

We have used the detection of S-100 protein to address several other practical problems. Paget's disease of the nipple seldom presents diagnostic problems. But extramammary Paget's disease may be difficult to separate from pagetoid (superficial spreading) melanoma in situ, especially when the Paget's disease tissues contain substantial amounts of melanin or the pagetoid melanoma is amelanotic. The conventional approach to separating these conditions is to stain for mucins; this is effective in a proportion of patients, Paget's disease being positive and pagetoid melanoma negative. Results with mucin stains are sometimes equivocal, however, especially in patients with mammary Paget's disease. We are studying a group of patients with extramammary Paget's disease or with pagetoid melanoma for the presence of S-100 protein in their intraepidermal tumor cells (B. Glasgow, MD, Department of Pathology, UCLA, unpublished data, April 1986). This is an effective method of separating these two diseases, Paget's disease being often mucin-positive to some degree and always S-100 protein-negative, whereas pagetoid melanoma is usually mucin-negative and S-100 protein-positive.

As another example of a practical application of staining with anti-S-100 protein serum, we have determined that a small number of tumor cells, invisible on conventional hematoxylin and eosin staining of the tissues, can be detected with this reagent. This has obvious practical applications in the search for micrometastases. We recently reported the results

of a study of the regional lymph nodes of patients with melanoma using this approach.[39] Sections of 1,273 nodes from 58 patients with melanoma were stained in an immunoperoxidase assay using an antiserum to S-100 protein and aminoethyl carbazole as indicator. Using hematoxylin-eosin stain, 128 of these nodes (10%) were seen to contain melanoma; using the anti-S-100 protein technique, 363 (29%) were found to be tumor-positive. The additional tumor-positive nodes contained single tumor cells or small groups of tumor cells and were adjacent to nodes that were partly or wholly replaced by melanoma. The anti-S-100 protein approach identified more accurately those patients who would die of recurrent melanoma less than five years after lymphadenectomy.

We have also examined lymph nodes from patients who underwent lymphadenectomy for stage I disease. These were persons in whom tumor metastases were likely to develop, as assessed by the micrometer measured thickness of the primary tumor. We have thus far examined 470 lymph nodes from 25 patients with stage I disease. The incidence of occult metastasis in this group of patients is substantially less than that in the patients with histologically confirmed stage II disease. Nonetheless, 12% of patients, who were judged to have tumor-free lymph nodes on hematoxylin-eosin staining, had tumor in the lymph nodes on S-100 protein assessment. Studies in progress are designed to assess the clinical aspects of the patients with stage I disease who have occult metastasis and the histopathologic characteristics of their tumors. If a subset of patients can be identified in which there is a high likelihood of occult metastasis, this would provide a rational basis for elective lymph node dissection.

Most studies of S-100 protein distribution have used a polyspecific antiserum. Monoclonal antibodies to the whole S-100 protein molecule and its subunits are, however, now becoming available. These reagents have the advantage of being able to separate different tissue subtypes and their diseases. Monoclonal antibodies to melanoma-associated antigens are available[40] and can, in different situations, represent a supplement or alternative to S-100 protein studies. In our experience, the polyspecific anti-S-100 protein serum is more robust for practical application and more widely applicable, especially to paraffin-embedded formalin-fixed material.

The Use of Immunoperoxidase Techniques in Diagnosis and Classification of Lymphoproliferative Disorders

FARAMARZ NAEIM, MD:* The immunophenotypic characterization of the cellular elements in lymphoid tissues is of great value in diagnosis and classification of lymphoproliferative disorders. The results of immunophenotypic studies, however, should always be incorporated with other available data, such as clinical findings, histologic observations, enzyme cytochemical stains, cytogenetic studies and results obtained from culture studies and DNA-complementary DNA probes. This is the only proper way to reach a more definitive conclusion.

Various techniques are available for screening and evaluating reactivity of monoclonal and highly specific antibodies against lymphoid tissues. The most popular ones are immunoperoxidase and fluorescence (fluorescent microscopy and flow cytometry) techniques.[41-47] We shall present the use of immunoperoxidase techniques to diagnose and classify lymphoproliferative disorders.

Most of the antibodies used as markers to identify the stage of differentiation in the lymphoid pathway are raised against cell membrane integral proteins (Figure 3). In the fixed paraffin-embedded tissues, most of the cell membrane-associated proteins may change to a significant degree. Tissue processing, especially exposure to organic solvents,[48] will also alter immunoglobulin phenotypes and may lead to spurious results even when cytoplasmic immunoglobulins are studied. Several reports indicate that transport medium (Michael's medium) preserves the antigenicity of the cell markers in the lymphoid cells and thus is a suitable medium for transporting lymphoid tissues when immediate preparation of the tissue for immunologic studies is not possible.[49,50] Our experience confirms the report by Sheibani and Tubbs, however, that the specimens placed in Michael's transport medium may generate unreliable results for the B-cell differentiation antigens,[51] whereas preservation of the T-cell antigens is often satisfactory. Fresh or fresh frozen (−75°C) tissues are the most suitable for immunophenotypic studies on the lymphoid system.

The approach of pathologists for the use of monoclonal and highly specific antibodies in lymphoproliferative disorders is as follows:

Differential Diagnosis

Immunophenotypic studies are of tremendous help in distinguishing non-Hodgkin's lymphomas from certain difficult cases of reactive hyperplasia (for example, follicular lymphomas versus follicular hyperplasia). Virtually all non-Hodgkin's lymphomas are the result of clonal proliferation of lymphoid cells at a particular stage of lymphoid differentiation and thus are monoclonal phenotypically.

In lymphoid hyperplasia, various subsets of lymphoid elements are involved and the result is a polyclonal expression of the cell markers. In follicular hyperplasia, the germinal centers show scattered L^+, K^+, immunoglobulin (Ig) M^+ and IgG^+ cells surrounded by a heavily stained mantle zone of lymphoid cells that are usually L^+, K^+, IgM^+ and IgD^+. There are usually more K^+ than L^+ cells, with an approximate ratio of 2:1. Most of the cells in paracortical areas are T lymphocytes, and in most reactive conditions (except the acquired immunodeficiency syndrome [AIDS]), the ratio of helper/inducer T lymphocytes ($T4^+$/Leu 3^+) to suppressor/cytotoxic T lymphocytes ($T8^+$/Leu 2^+) is usually greater than one. In patients with AIDS, the T4-T8 ratio is low because $T4^+$ cells become infected by the human T-lymphotropic virus type III through their T4 receptors.[52] One of the prominent morphologic features in AIDS-related lymphadenopathy is infiltration of the follicular structures by $T8^+$ cells with evidence of focal follicular destruction and degeneration of interdigitating cells.[53] Another frequent finding is the presence of clusters of monocytoid cells in the sinusoids.[54] These monocytoid cells appear to be B lymphocytes and to stain polyclonally for B-cell markers.

Reactive lymph nodes also contain various numbers of macrophages (histiocytes) in follicular as well as interfollicular areas. Histiocytes stain with certain monoclonal

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markers, such as Leu M1 and Leu M3 as well as lysozyme (muramidase) and α-antitrypsin.

Not infrequently, when pathologists are dealing with extranodal malignant small cell neoplasms, they may have difficulty in making a definitive diagnosis based on hematoxylin and eosin slides. In such cases, hematopoietic markers (such as T-200 and common leukocyte antigens) and markers for intermediate filaments (keratin) will help to put the malignant tumor into the hematopoietic (lymphoid) or nonhematopoietic categories.

Classification

Cell markers also play an important role in the classification of the lymphoproliferative disorders. We shall present their possible use in the classification of lymphomas and lymphoid leukemias. Immunohistochemistry provides valuable information about the extent (partial or total) of lymph node involvement, pattern of involvement (diffuse or nodular), cell type (B lymphocytes versus T lymphocytes) and proportion of nonneoplastic lymphoid elements.

The monoclonality of the B-cell lymphomas is usually based on the expression of one immunoglobulin light chain. Immunoglobulin heavy chains are also of monoclonal origin in most, but not all, of the cases of lymphoma. Most of the B-cell lymphomas, according to their immunophenotypic expression, fall into the middle of the B-lymphocyte differentiation pathway and thus are usually TdT^- (terminal deoxynucleotidyl transferase-negative), $BA2^-$, $B1^+$, $B4^+$ and SIg^+. The pattern, however, of the reactivity of the B-cell monoclonal antibodies in lymphomas may not exactly match with the steps of differentiation of the normal B-lymphocyte lineage. For example, some of the follicular lymphomas (B cells) express the common acute lymphocytic leukemia antigen (T5, BA3), which in normal conditions is expressed in pre-B cells (CI^+SIg^-), or there is a significant overlap on the phenotypic expression in some of the subclasses of lymphomas, such as large noncleaved, small noncleaved (Burkitt's) and immunoblastic lymphomas.

The identification of clonal proliferation in T-cell lymphoid malignant diseases by the available monoclonal markers is difficult because T-cell malignant disorders may express a mixture of helper (T4/Leu 3) and suppressor (T8/Leu 2) cells. In malignant conditions, however, the ratio of these two subtypes is usually way off the normal ratio (T4/T8 = 2). The T-cell lymphomas, especially the post-thymic (peripheral) variants, may express receptors (such as Ia) that do not correspond to their extent of differentiation.

The immunophenotypic studies on tissue sections will provide information about the relative proportion of nonneoplastic elements in the involved tissue. For example, most of the B-cell lymphomas, especially follicular types, contain a significant number of T cells.[55] This nonneoplastic contamination of the tissue samples may generate confusing results in cell-suspension studies. The result of cell-suspension studies should, therefore, always be correlated with the morphologic examination and immunoperoxidase results on the tissue sections.

Immunoperoxidase studies in Hodgkin's disease have a limited value because the pattern of reactions, similar to the reactive nodes, is polyclonal. When the problem, however, is distinguishing lymphocyte-predominant Hodgkin's disease from small lymphocytic cell (well-differentiated) lymphoma, immunoperoxidase staining is helpful. Most of the lymphocytes in lymphocyte-predominant Hodgkin's disease are T cells with a preponderance of the helper cell phenotype (T4/T8 ratio < 1), whereas lymphoid cells in almost all small lymphocytic lymphomas are monoclonal B cells. Another difficult area is the differential diagnosis between Hodgkin's disease and some variants of peripheral T-cell lymphomas (such as pleomorphic T-cell lymphoma) where large binucleated or multinucleated Reed-Sternberg-like cells are present. It has been reported that Leu M1, a receptor present on monocyte-granulocyte series, is also present on Reed-Sternberg cells.[56,57] Recent studies, however, show that Leu M1 is also present on activated lymphocytes as well as malignant T cells.[58] Table 2 shows several monoclonal antibodies used for the diagnosis and classification of lymphomas.

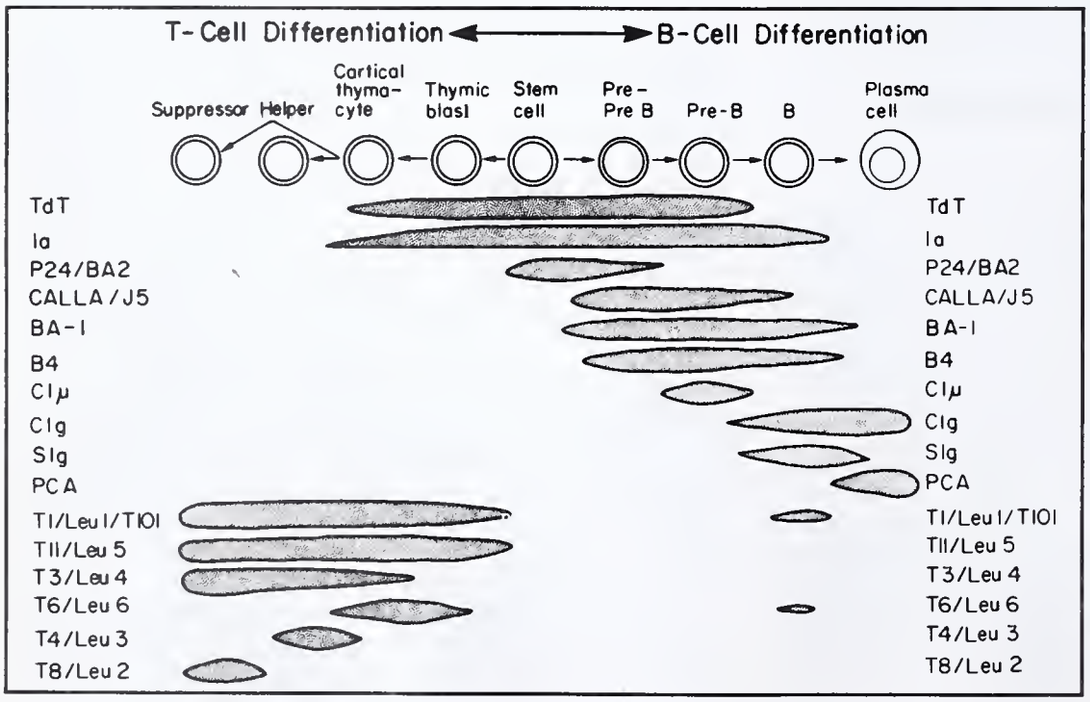

Figure 3.—Phenotypic characteristics of lymphocytes in various stages of differentiation. CALLA = common acute lymphocytic leukemia antigen, Ia = immune-response antigen, PCA = passive cutaneous anaphylaxis, TdT = terminal deoxynucleotidyl transferase

Lymphoid leukemias, unlike lymphomas, represent a broad spectrum of phenotypic expressions that correspond well to the normal differentiation pathway in the lymphoid system. Classification of the lymphoid leukemias based on their immunophenotypic characteristics, such as null, pre-pre B (common acute lymphocytic leukemia), pre-B, B and T, is well accepted and widely used by hematologists and hematopathologists.[59-61] Cell marker studies on patients with leukemia are usually done on cell suspensions (specimens of peripheral blood, bone marrow aspirate or body fluid) by immunofluorescent techniques (flow cytometer, fluorescent microscope). When the samples contain a small percentage of tumor cells, however, and morphologic examinations are necessary for interpreting the results, the immunoperoxidase technique plays an important role. This technique is applied to smears or cytocentrifuged and touch preparations. The immunoperoxidase technique is also helpful when the only available specimens are solid tissues (bone marrow biopsy specimens, lymph nodes). Bone marrow biopsy specimens should be prepared fresh or fresh frozen without any decalcification. The results of immunoperoxidase stains on bone marrow biopsy specimens should be interpreted carefully with the presence of proper positive and negative controls because of the frequency of background staining. Table 3 lists several monoclonal antibodies that are helpful in the diagnosis and classification of lymphoid leukemias.

TABLE 2.—*A Simplified Panel of Markers Recommended for Lymphoma Workup**

Hematopoietic	*T-200/Common Leukocyte Antigen*
B cell	
Pan B	B4, BA1, Ix
B subtype	Immunoglobulin heavy and light chains
T cell	
Pan T	T3/Leu 4, T11/Leu 5
T subsets	T4/Leu 3, T8/Leu 2
Others	Leu M1, CALLA, TdT

CALLA = common acute lymphocytic leukemia antigen, TdT = terminal deoxynucleotidyl transferase

*Many other monoclonal antibodies are available for further characterization of tumor cells.

TABLE 3.—*A Simplified Panel of Markers Recommended for Lymphoid Leukemia Workup**

Acute Leukemia	
	TdT
	CALLA/55
	B4, BA1
	Immunoglobulin heavy and light chains
	T11, Leu 4
	T6
	T4/Leu 3, T8/Leu 2
Chronic Leukemia	
	Ia
	B4, BA1
	Immunoglobulin heavy and light chains
	T11, Leu 4
	T6
	T4/Leu 3, T8/Leu 2
Chronic Leukemia	
	Ia
	11B4, BA1
	Immunoglobulin heavy and light chains
	T11, Leu 4
	T6
	T4/Leu 3, T8/Leu 2

CALLA = common acute lymphocytic leukemia antigen, Ia = immune-response antigen, TdT = terminal deoxynucleotidyl transferase

*Many other monoclonal antibodies are available for further characterization of tumor cells.

Immunohistochemical Staining for Intermediate Filaments in Cytodiagnosis

JONATHAN W. SAID, MD:* Intermediate filaments are long, unbranching cytoplasmic filaments 10 nm in diameter that can be differentiated from 5- to 7-nm microfilaments and 21-nm microtubules that make up the cytoskeleton of mammalian cells. The finding that different tissues have distinct profiles of intermediate filaments that may be maintained with neoplastic expression and metastasis has led to widespread use of antiserum to intermediate filaments and related proteins in tumor diagnosis and characterization.[62,63] Ultrastructurally, different types of intermediate filaments are indistinguishable; immunochemically, however, they may be divided into five subclasses (Table 4).

Technical Considerations

Several polyclonal and monoclonal antibodies are now commercially available for intermediate filament localization. Specimens suitable for immunostaining include cytologic preparations and fine needle aspirates, frozen sections and even routine alcohol or paraformaldehyde-fixed and paraffin-embedded tissues. Whether intermediate filaments can be found depends on the nature of the tissue, the type of histologic preparation and the immunohistochemical technique. To show sparse quantities of intermediate filaments in some situations (for example, keratin proteins in formalin-fixed sections of most adenocarcinoma tissue), preliminary

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TABLE 4.—*Distribution of Intermediate Filaments in Mammalian Cells and Tumors*

Filament	*Normal Distribution*	*Tumors*
Keratin (40 to 68 kd)	All epithelial cells, including liver and pancreas; mesothelial cells	Carcinomas; mesotheliomas
Vimentin (57 kd)	Mesenchymal cells, including endothelial cells, lymphocytes, macrophages, fibroblasts	Sarcomas
Desmin	Muscle cells (smooth, skeletal and cardiac muscle)	Leiomyosarcomas; rhabdomyosarcomas
Glial filaments (51 kd)	Glial cells	Astrocytomas; ependymomas
Neurofilaments (68,145,200 kd)	Neurons	Neuroendocrine tumors

kd = kilodalton

proteolytic digestion may be essential to expose antigenic sites.[64]

Keratin Proteins in Tumor Diagnosis

Human cytokeratins are a large family of proteins ranging in molecular weight from 40 to 68 kilodalton (kd) that have proved useful in diagnostic surgical pathology as markers of epithelial derivation in neoplastic cells.[65,66] Different keratins are the product of a family of genes that determine their expression during embryonal development and postnatal maturation. Because different epithelia show specific profiles of keratin proteins (which may be maintained with neoplastic expression), antibodies directed at individual keratins offer a novel tool for tumor characterization.

In adult epidermis, low-molecular-weight keratins (45 and 46 kd) are located in the basal layer and a transition to larger keratins (55 to 68 kd) represents a commitment to differentiation in the suprabasal layers. This pattern is recapitulated in epidermoid carcinomas of the skin and other sites. Infiltrating squamous cell carcinomas stain predominantly for low-molecular-weight keratins (45 and 46 kd), and staining for large keratins (62 to 67 kd) is restricted to differentiated areas of tumors.[67] Basal cell carcinomas, as may be expected, stain for low-molecular-weight keratins (45 and 46 kd) with virtual absence of large keratins.

Although nonstratified epithelia, such as the columnar epithelium of the gastrointestinal tract, have a simple cytokeratin composition, human bronchus displays a complex pattern of cytokeratins, which is recapitulated in the diversity of cytokeratins expressed by lung tumors. Squamous cell carcinomas are characterized by cytokeratins of 45, 46 and 55 kd, with immunostaining for 63-kd keratin restricted to well-differentiated or keratinizing areas.[68] This differs from staining in adenocarcinomas and oat cell carcinomas, in which low-molecular-weight keratins predominate. Staining for keratins may also be useful in making the differential diagnosis between adenocarcinoma and mesothelioma. Although they have histologic similarities, these tumors differ in the profiles of cytokeratins that they express[68,69] and in the patterns of staining (diffuse and perinuclear in mesotheliomas, peripheral in adenocarcinomas).[70]

Vimentin Filaments in Tumor Diagnosis

Vimentin filaments are characteristically present in the cytoplasm of mesenchymal cells and neoplasms of mesenchymal derivation. In addition, vimentin is a cytoskeletal protein of many immature cells and in some systems may be a differentiation marker lost as cells mature and synthesize other proteins.[71] Once exfoliated into body fluids, exfoliated cells may acquire the ability to produce a second cytoskeleton composed of vimentin. A certain time period may be required before vimentin coexpression occurs in tumor cells after they lose contact with their neighbors or are removed from solid tissues in the course of metastasis. The presence of this additional cytoskeleton may influence mitotic activity and affect the growth rate and aggressive behavior of the tumor. Although solid epithelial tumors generally express only cytokeratins and sarcomas and lymphomas vimentin, exceptions include the coexpression of keratin and vimentin in mesothelial cells and mesotheliomas and the presence of cytokeratins in unusual sarcomas, such as epithelioid[72] and synovial cell sarcomas.[73]

Glial Filaments, Desmin and Neurofilaments in Tumor Diagnosis

Filaments specific for astroglial cells, muscle cells and neurons, respectively, have proved valuable aids in cell identification (Table 4). Glial filaments are useful markers for malignant gliomas, including glioblastoma multiforme and gliosarcoma, and may also be present in ependymomas. Desmin is found in smooth, skeletal and cardiac muscle and is a useful marker for leiomyosarcomas and rhabdomyosarcomas of all types, including embryonal and alveolar soft part sarcomas. Neurofilaments are also present in some neuroendocrine cells and their tumors, including carcinoid tumor, medullary carcinoma, pheochromocytoma and esthesioneuroblastoma. The presence of cytokeratins and the absence of neurofilaments in tissue sections[74,75] and aspirates (unpublished observations, April 1985) from small-cell anaplastic carcinomas of the lung support the endodermal derivation of all types of lung carcinoma and explain the mixtures between small-cell carcinomas and other cell types.

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Digitalis Toxicity—Turning Over a New Leaf?

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

LLOYD H. SMITH, JR, MD:* *It is routine to ask each chief medical resident at Moffitt Hospital to present a medical staff conference near the completion of his or her tour of duty in that important position. Not only does this tradition make us the beneficiaries of scholarly reviews, it also allows us the chance to express publicly our gratitude for a job well done. Dr Satinder Bhatia is completing four years as a member of this house staff, to which he came after his graduation from Emory University School of Medicine in Atlanta. From here he will go to the Brigham and Women's Hospital in Boston to pursue specialty training in cardiology. He has brought intelligence, dedication, maturity and style to this year of chief residency. We wish him the best in his new career. We look forward to a discussion that presages his career in cardiology—a review of digitalis toxicity.*

SATINDER J.S. BHATIA, MD:† Although it has been 200 years since the publication of the classic *Account of the Foxglove* by William Withering, MD, the efficacy of digitalis glycosides as positive inotropes continues to be debated. Withering's caution of the potential for digitalis toxicity is uncontested, however. His often-quoted description of digitalis toxicity states

> The foxglove, when given in very large and quickly repeated doses, occasions sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow, increased secretion of urine with frequent motions to part with it and sometimes inability to retain it, slow pulse, even as low as 35 in a minute, cold sweats, convulsions, syncope, death.[1]

It is the objective of this review to update the manifestations (and management) of digitalis excess so accurately recorded 200 years ago.

I will focus primarily on toxicity due to long-term digoxin therapy. Digoxin is currently the fifth most prescribed drug in the United States. The drug has a high toxic-therapeutic ratio, with surveys of inpatients and outpatients showing an incidence of toxicity ranging from 6% to 29%.[2,3] Recognition of toxicity is imperative because the continuation of digoxin therapy has a high mortality. It appears that physician education is contributing to a decrease in the incidence and morbidity of toxicity, but toxicity continues at an unacceptably high rate.

Digoxin Pharmacokinetics

Digoxin tablets are passively absorbed from the small intestine, with effective absorption of 55% to 75%. Encapsulated liquid digoxin has an absorption rate of 90% to 100%.[5] Excretion of digoxin is primarily by glomerular filtration with a small element of hepatic metabolism and active tubular secretion.[4] The average elimination half-life is 1.5 days; it is prolonged in persons with a decreased glomerular filtration rate and slowed with acute massive ingestion. Protein binding of digoxin is in the range of 20% to 25%.[5]

The time course for achieving therapeutic concentrations varies with the route of administration. The serum concentration of digoxin rises more rapidly after intravenous than after oral administration.[4] Maintenance dose administration without a preceding loading regimen leads to steady-state levels in five to seven days. Although the administration of a loading dose more rapidly achieves therapeutic digoxin concentrations, the risk of toxicity is much increased. If administered intravenously, the dose of digoxin should be two thirds the dose given orally. The equivalent dose of the encapsulated elixir is three fourths the oral dose in milligrams. Dosage in obese patients should be based on lean body mass and not total body weight due to the minimal distribution of digoxin to adipose tissue.

Prevalence of Digoxin Toxicity

In Withering's era the prevalence of digitalis toxicity was estimated at 18% to 25%.[2] In the 1970s the reported incidence varied from 20% to 30%.[3] The incidences reported in the 1980s are lower, with prevalences of 6% to 18%.[2] The reasons for this trend may include the availability of the means to measure serum digitalis levels and the education of physicians in pharmacokinetics.[4]

Measuring and Interpreting Serum Digoxin Levels

The radioimmunoassay for digoxin became available in 1969 and defined the therapeutic range as 0.5 or 0.8 to 2.0 ng per ml.[6] The optimal time for measurement is just before the

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ABBREVIATIONS USED IN TEXT

AV = atrioventricular
Ig = immunoglobulin
PAC = premature atrial complex
PVC = premature ventricular complex

next dose, or at least six hours after an oral dose and four hours after intravenous administration.[4] The ratio between myocardial and serum digoxin levels is fairly constant despite variation in total body digoxin content, providing a rationale for the use of serum levels to reflect myocardial content.[7] The causes of false-positive assays include spironolactone, hyperbilirubinemia, circulating γ-emitting radioimagers and renal failure. More than 60% of patients with chronic renal failure have been reported to have false-positive assay results to 1.0 ng per ml, possibly due to an endogenous circulating digoxin-like substance.[8]

Interpreting serum digoxin measurements has been hampered by the prevalence of two myths: one, a normal serum digoxin level implies that digoxin toxicity is absent and, two, an elevated serum digoxin level implies that digoxin toxicity is present. In a review of more than 1,000 patients, the mean serum digoxin level in nontoxic patients was 1.4 ng per ml, with the levels in patients with toxicity being twofold to threefold higher, but there was considerable overlap between the two groups of patients.[5] Approximately 10% of patients without toxicity had serum digoxin values of 2 to 4 ng per ml; 10% of patients with toxicity had serum concentrations of digoxin of less than 2 ng per ml.[9] Bayesian analysis reveals that the higher the serum digoxin level, the higher is the likelihood of toxicity.[10] For example, the risk of toxicity at a digoxin concentration of higher than 3.0 ng per ml was 12-fold the risk at a serum concentration of 0 to 0.99 ng per ml. Patients in atrial fibrillation are more resistant to digoxin toxicity and often require "toxic" doses for adequate rate control. Toxicity may appear on conversion to sinus rhythm. The diagnosis of digitalis toxicity is a clinical one, with serum digoxin values providing only part of the diagnostic information. The significance of a given digoxin value depends on the underlying tolerance of the myocardium to digitalis. Thus, although no serum digoxin level proves or disproves toxicity, a level higher than 3.0 ng per ml in the appropriate setting lends strong support to a diagnosis of digitalis excess.

Digitalis-Drug Interactions

Many drugs have been reported to affect digoxin absorption.[5,11,12] This problem has been minimized by the use of more bioavailable preparations. Concurrent administration of antacids, bran, kaolin pectate, cholestyramine resin, colestipol hydrochloride, activated charcoal, sulfasalazine, neomycin or *para*-aminosalicylic acid can decrease digoxin absorption. This is minimized by administering digoxin two hours before the drug in question. Withdrawing the interacting drug without decreasing the digoxin dose can lead to enhanced absorption and toxicity. Increased intestinal motility due to the use of metoclopramide hydrochloride or cathartics may decrease digoxin absorption, whereas agents that decrease motility (atropine, propantheline bromide) have the opposite effect. Malabsorption and mucosal damage by cytotoxic drugs can decrease digoxin absorption as well.

Many drugs are reported to increase serum digoxin concentration. Quinidine causes such an increase in more than 90% of patients.[13] The effect is variable and ranges from none to sixfold, with an average increase in serum digoxin levels of twofold. This is due to a decrease in renal and nonrenal clearance and in the volume of distribution of digoxin. It has been postulated that the early rise in serum digoxin levels is due to displacement of digoxin from tissue stores, but the myocardial-serum digoxin ratio remains constant.[14] Studies in animals show that the increased serum digoxin concentration is not accompanied by a proportional increase in digoxin effect, as measured by percent inhibition of rubidium 86 uptake. Because total myocardial digoxin content increases appropriately, this implies that digoxin may be selectively displaced from active myocardial binding sites.[14]

The calcium channel blockers have a variable effect on serum digoxin concentration. Verapamil increases digoxin levels in more than 90% of patients by decreasing clearance and perhaps the volume of distribution of digoxin.[15] Nifedipine has no effect on serum digoxin levels and diltiazem hydrochloride causes a small but significant increase.[16] Amiodarone increases serum digoxin concentration by twofold by decreasing the clearance without changing the volume of distribution.[17] The increased digoxin concentration may be accompanied by signs and symptoms of digoxin toxicity. Other agents that can increase the serum digoxin concentration include spironolactone (inhibition of active tubular digoxin secretion) and antihypertensive agents (decreased renal blood flow and glomerular flow rate). Antibiotic therapy has an important effect in 10% of patients on digoxin therapy, perhaps because antibiotics eliminate the gastrointestinal bacteria that break down a proportion of ingested digoxin.[18] This effect appears minimal with the encapsulated elixir preparations. Thus, several commonly used drugs can increase the serum digoxin concentration and precipitate digoxin toxicity.

Factors Affecting Myocardial Sensitivity to Digoxin

Many conditions can precipitate digitalis toxicity (Table 1), either by decreasing the clearance or volume of distribution of digoxin—that is, increased serum digoxin concentration—or by decreasing myocardial tolerance for digoxin.[19] Renal failure is the most common reason for a rise in the serum digoxin level due to decreased renal excretion and volume of distribution. The loading and maintenance doses of

TABLE 1.—*Factors Affecting Myocardial Tolerance to Digitalis Glycosides*

Renal failure
Advanced age
Hypothyroidism/hyperthyroidism
Hypokalemia
Hypomagnesemia
Hypercalcemia, severe
Chronic pulmonary, heart disease
Cardiac disease—myocarditis, myocardial infarction, cardiomyopathy
CNS processes, such as cerebrovascular accidents
Decreased lean body mass (muscle digoxin depot)
Extracorporeal circulation
Concomitant drug administration

CNS = central nervous system

digoxin must, therefore, be reduced and the serum digoxin concentration monitored. Dialysis removes only a small fraction of total body digoxin stores. A supplemental digoxin dose after dialysis can increase the serum concentration of digoxin and cause toxicity. Patients of advanced age are more susceptible to toxicity due to an age-dependent decrease in glomerular filtration rate and renal digoxin excretion, decreased lean body mass and thus volume of distribution of digoxin and a possible increase in myocardial sensitivity to digoxin. Hypothyroidism increases serum digoxin concentration by decreasing the glomerular filtration rate and volume of distribution of the digoxin. The myocardium of patients with myxedema may have a reduced tolerance for digoxin. These changes are reversed with thyroid replacement. Hyperthyroid patients, on the other hand, have reduced serum digoxin levels due to an increase in renal digoxin clearance (glomerular filtration rate).

Electrolyte imbalance may also precipitate digoxin toxicity. Burch has defined a "digoxin-diuretic" cardiomyopathy to highlight the risk of diuretic-induced hypokalemia in patients receiving digoxin.[20] This concept can be extended to include diuretic-induced hypomagnesemia and hypercalcemia. Hypercalcemia can precipitate digoxin toxicity, but only at very high levels that may be transiently achieved during intravenous administration of calcium. Hypocalcemia increases myocardial digoxin tolerance. Intracellular hypokalemia can exist with normal serum potassium levels, with metabolic alkalosis serving as a clue to total body potassium depletion. Potassium competes with digitalis for myocardial receptor binding sites, and hypokalemia results in an increase in myocardial digoxin uptake, a decrease in sodium-potassium pump activity (increased digoxin binding to the sodium-potassium pump) and a decrease in tubular secretion of digoxin. The amplitude of digoxin-induced delayed afterdepolarizations is increased, and digoxin-induced atrioventricular (AV) conduction delay is prolonged. Thus, toxicity is seen at lower serum digoxin levels in the presence of hypokalemia.[21]

In digoxin-treated patients, hypomagnesemia is currently more common than hypokalemia. The causes include malabsorption of magnesium due to splanchnic vessel congestion, renal wasting due to hyperaldosteronism and diuretic therapy (blocked by potassium-sparing diuretics: spironolactone, triamterene, amiloride hydrochloride) and digoxin-induced impairment of tubular reabsorption of magnesium.[22] Like hypokalemia, hypomagnesemia increases myocardial digoxin uptake, decreases activity of the sodium-potassium pump and increases the amplitude of digoxin-induced afterdepolarizations. Hypomagnesemia can also exist with normal serum levels and can cause intracellular hypokalemia that is refractory to potassium replacement. Therapy for digitalis toxicity should thus include repletion of both potassium and magnesium stores. Thus, decreased magnesium stores, in a manner akin to hypokalemia, can precipitate digoxin toxicity at therapeutic levels.

Chronic pulmonary disease is a well-identified precipitant of digitalis toxicity.[5,23] Factors contributing to this include hypoxia, hypercapnia, endogenous and exogenous catecholamines, hypokalemia, vagotonic (suctioning, acidosis, infections) and vagolytic (atropine) stimuli, advanced age and decreased lean body mass. Underlying severe cardiac disease (myocarditis, myocardial ischemia or infarction, cardiomyopathy/amyloidosis) also reduces the myocardial threshold for toxicity. Acute cerebrovascular accidents can precipitate toxicity by increasing central sympathetic outflow. Extracorporeal circulation may increase myocardial sensitivity in the first 24 hours after an operation. Concomitant drug therapy may potentiate the cardiac effects of digitalis. Administering sympatholytic, vagotonic or sympathomimetic medications may increase digoxin conduction block and ectopic impulse formation. Patients with sinus node dysfunction are particularly sensitive to combination antiadrenergic therapy, such as with clonidine, methyldopa, reserpine and β-blockers. Succinylcholine chloride decreases, while halothane increases, myocardial digoxin tolerance. Finally, although digoxin pharmacokinetics are normal in patients with cirrhosis, patients with obstructive jaundice may be more sensitive to the vagotonic effects of digoxin, possibly due to retained bile acids with a structural similarity to digoxin.

Digitalis and Myocardial Infarction

Myocardial ischemia and infarction are generally accepted as causing a decrease in myocardial tolerance to digoxin. Although several clinical studies have failed to show that an acutely infarcted myocardium is more susceptible to digitalis arrhythmias,[24] studies in animals have clearly shown that ischemic myocardium is more sensitive to digitalis toxicity, with the site of initiation of digitalis-induced ventricular tachycardia being localized to the infarcted and peri-infarcted area.[25] Compounding this increased potential for toxicity is the finding that digoxin is a weak inotrope for the treatment of peri-infarction congestive heart failure. The reasons for a lack of significant digoxin effect include digoxin-induced peripheral vasoconstriction (increased afterload) and bulging of the ischemic or infarcted myocardium with decreased effective forward cardiac output. Digoxin may also cause coronary vasoconstriction and an increase in myocardial oxygen demand; digoxin has been shown to increase the size of experimental myocardial infarction.[26] Thus, in the setting of peri-infarction congestive heart failure, digoxin has possible enhanced toxicity and limited efficacy as an inotrope and may worsen myocardial ischemia.

The effect of digoxin therapy on survival after myocardial infarction is likewise controversial. Three nonrandomized studies show the use of digoxin to be an independent risk factor for mortality,[27-29] but more recent reports were unable to assign any additional mortality risk to its use.[30,31] In all the studies, the patients receiving digoxin were hemodynamically more compromised. Definition of the role of digoxin therapy in the peri-infarction period must thus await the outcome of randomized trials.

Extracardiac Symptoms of Digitalis Toxicity

The extracardiac symptoms of digoxin excess are nonspecific and are often mistakenly attributed to underlying congestive heart failure, thus delaying recognition. Lely and Van Enter reported that 28% of patients had symptoms for more than three weeks before diagnosis.[32] In as many as 50% of patients, cardiac arrhythmias are not preceded by extracardiac symptoms. There is a poor correlation between serum digoxin concentration and the extent of symptoms, although in general, as the serum digoxin level rises, so does the prevalence of symptoms. Symptoms are primarily of the ocular,

neuropsychiatric and gastrointestinal systems. The goals of clinical diagnosis are to identify the subgroup of patients with digoxin toxicity but without extracardiac symptoms, and the subset without toxicity who have the symptoms attributable to toxicity.

Of the extracardiac manifestations, anorexia is often the earliest symptom and is followed in two to three days by nausea and vomiting due to stimulation of the area postrema of the medulla. Abdominal pain and bloating may be nonspecific symptoms or may be due to nonocclusive mesenteric ischemia from digitalis-induced vasoconstriction. Such ischemia may be relieved by verapamil. Ocular symptoms (alteration of red and green perception, predominance of yellow-green vision), consistent with a diagnosis of retrobulbar neuritis, may persist for two to three weeks after digitalis therapy is discontinued. Neuropsychiatric symptoms range from ubiquitous neuromuscular complaints (fatigue, muscle weakness) and subtle alterations of personality to outright delirium and psychosis, often termed "foxglove frenzy" or "digitalis delirium."

Significant digitalis toxicity may produce hyperkalemia that can be refractory to therapy. The level of potassium elevation is directly correlated with mortality.[33] Mechanisms include total body inhibition of the sodium-potassium pump and increased congestive heart failure with decreased glomerular filtration rate. Hyperkalemia can worsen digitalis-induced AV block and increase the pacing threshold of a ventricle with a digitalis toxic reaction.[34]

Cardiac Manifestations of Digitalis Toxicity

Increased congestive heart failure may be the initial manifestation of toxicity in as many as 7.5% of patients.[35,36] This may occur independent of arrhythmias or ischemia and subsides with discontinuation of digitalis therapy. Rapid intravenous digoxin administration can abruptly increase afterload via peripheral vasoconstriction and precipitate pulmonary edema. Digitalis-induced dysrhythmias may produce palpitations, angina, syncope or a low-output state. In the setting of atrial fibrillation, a subtle alteration of the cardiac rhythm may be the only clue to toxicity.

Digitalis-Induced Dysrhythmias

Many of the toxic effects of digitalis are mediated via the autonomic nervous system (Table 2).[5,37,38] At the level of the sinus node, atrial myocardium and AV node, the primary digitalis effect is parasympathomimetic and antiadrenergic. Adrenergic stimulation is the primary cause of toxicity at the level of His-Purkinje fibers and ventricular myocardium. Delayed afterdepolarizations seen in atrial fibers, Purkinje's fibers and ventricular muscle are transient late depolarizations that follow repolarization of the action potential. Inhibition of the sodium-potassium pump by digitalis leads to increased intracellular sodium, which in turn leads via the sodium-calcium exchange system to an increase in intracellular calcium. The calcium overload triggers an oscillatory release of calcium from intracellular stores and a secondary transient inward current of sodium resulting in the afterpotentials. If of sufficient amplitude, the afterpotentials can trigger another action potential and result in coupled beats or tachycardia, referred to as triggered activity.[5,38] Amplitude of the afterpotentials can be increased by digitalis, hypokalemia, hypercalcemia and catecholamines (via a β-receptor-mediated increase in intracellular calcium) and reduced by manganese, magnesium and verapamil. At the ventricular level, ectopy may also be due to enhanced automaticity (accelerated phase 4 depolarization) and reentry mechanisms.

Dysrhythmias, often multiple, occur in 80% to 90% of patients with digitalis toxicity.[35] Approximately a third of patients have arrhythmia as their initial manifestation of toxicity.[36] A characteristic feature of digitalis toxicity is the concurrent occurrence of enhanced impulse formation and depressed conduction.[39] Otherwise healthy patients primarily manifest deficits of conduction that are cholinergically mediated, whereas disorders of impulse formation with or without depressed conduction develop in patients with underlying myocardial disease.

Wellens has outlined four criteria for the electrocardiographic diagnosis of digitalis toxicity[39]: (1) appearance of a slow heart rate in a patient with a fast or normal heart rate; (2) appearance of a fast heart rate in a patient with a normal heart rate; (3) appearance of a regular rhythm in a patient with an irregular rhythm; (4) appearance of a regularly irregular rhythm. No arrhythmia is unique to digitalis toxicity. Any change in rhythm (or clinical state) in a patient receiving digitalis should suggest toxicity. Although a digitalis effect on the electrocardiogram has often been equated with toxicity, such changes may be present in the absence of toxicity and absent in two thirds of cases of toxicity.[35]

Table 3 catalogues the arrhythmias considered most suggestive of digitalis toxicity and those unlikely to be digitalis

TABLE 2.—*Mechanisms of Digitalis Toxicity*

Site of Action of Digoxin	*Toxic Electrophysiologic Effect*
Sinus node	Antiadrenergic, direct drug effect
Atrium	First-degree direct drug effect, increased automaticity, triggered activity
Atrioventricular node	First-degree direct effect, cholinergic
Purkinje's fibers and ventricular muscle	Increased automaticity, delayed afterdepolarizations, reentry mechanism

TABLE 3.—*Catalogue of Digitalis-Induced Arrhythmias*

Arrhythmias Most Suggestive of Digitalis Toxicity
- Bidirectional ventricular tachycardia
- Bigeminal ventricular rhythm
- Multiform premature ventricular complexes
- Atrial tachycardia with block
- Nonparoxysmal AV junctional tachycardia with or without exit block
- Supraventricular rhythm (atrial fibrillation) with ventricular ectopy
- Nonconducted premature atrial complexes
- Ventricular tachycardia with exit block

Arrhythmias Unlikely to Be Digitalis Induced
- Mobitz II second-degree AV block
- Parasystole
- Sinus tachycardia
- Paroxysmal AV junctional tachycardia
- Nonparoxysmal ventricular (idioventricular) tachycardia
- Multifocal atrial tachycardia
- Atrial flutter or fibrillation with rapid ventricular response
- Complete infranodal AV block
- Bilateral bundle branch block of varying degree

AV = atrioventricular

induced.[35,39-41] Nonparoxysmal AV junctional tachycardia is considered the most specific digoxin-induced arrhythmia. Bidirectional tachycardia, nonconducted premature atrial complexes (PACs) and bigeminal ventricular rhythm are virtually diagnostic of intoxication. Reviewed below are the most common digitalis-induced arrhythmias.

Disorders of Sinus Node Impulse Formation and Conduction

Disorders of sinus node impulse formation and conduction can manifest as sinus bradycardia or sinoatrial block (first, second [Mobitz I or II] or third degree), and a sudden reduction of the heart rate to less than 50 per minute is suggestive of toxicity.[35] Bradycardia is more common with acute overdose in patients without underlying heart disease, is cholinergically mediated and is reversible with atropine therapy.

Atrioventricular Block

Risk factors for the development of AV block include ischemic rheumatic disease, preexisting conduction system disease, a recent cardiac operation, acute inferior wall myocardial infarction and significant overdose in patients without underlying heart disease. First-degree AV block represents the earliest manifestation of toxicity, with a reported incidence of 15% to 25%; the actual incidence may be higher, as several authors do not consider it a manifestation of toxicity. The incidence of second-degree block is about 6%. Only Mobitz type I AV block has been reported. Third-degree AV block is uncommonly associated with syncope because of the acceleration of subsidiary pacemakers. The identification of retrograde P waves is a clue to this diagnosis because digitalis-induced AV block is often greater than ventriculoatrial block.[39]

Nonparoxysmal Atrioventricular Junctional Tachycardia

Nonparoxysmal AV junctional tachycardia represents up to 50% of digitalis-induced dysrhythmias and may be the most specific manifestation of toxicity. The ventricular response is 70 to 140 per minute, often occurs with exit block and may increase with exercise.[39] Carotid sinus massage produces minimal or no slowing of the rate. It is often precipitated by hypokalemia and is more common in the presence of underlying atrial fibrillation and advanced age. The differential diagnosis includes acute inferior wall myocardial infarction, rheumatic fever, a recent surgical procedure including coronary artery bypass grafting, anesthesia and myocarditis.[35] Therapy is indicated for hemodynamically significant tachycardia or a ventricular response of more than 90 per minute.[12]

'Paroxysmal' Atrial Tachycardia With Block

"Paroxysmal" atrial tachycardia with block, first described by Sir Thomas Lewis in 1906, accounts for 10% of digitalis-induced arrhythmias.[42] One third to one half of cases may be due to digitalis excess and 60% of these may be precipitated by recent hypokalemia. On examining the neck veins, the jugular a-wave rate is greater than the apical rate. The atrial rate is usually 150 to 250 with 2:1 AV block. Ventricular ectopy may be seen in 50% of cases. Carotid sinus massage may increase the degree of AV block. Prompt therapy is recommended because this arrhythmia has a reported mortality of 28% to 70%. The sequence of conversion is a decrease in the atrial rate, followed by 1:1 AV conduction and eventual conversion to sinus rhythm at a critical atrial rate.

Ventricular Ectopy

Ventricular ectopy is the most frequent digitalis-induced dysrhythmia, with a frequency of 50%. Premature ventricular complexes (PVCs) are nonspecific but some patterns are more suggestive of digitalis excess. These include multiform, bidirectional and bigeminal PVCs, as well as PVCs occurring after carotid sinus massage. Varying QRS morphology associated with a fixed PVC coupling interval is diagnostic of digitalis excess. The association of a supraventricular rhythm such as atrial fibrillation with complex ventricular ectopy is virtually pathognomonic of digoxin excess. Therapy is indicated for complex ectopy including multiform, "frequent," late diastolic (R on T), bigeminal and bidirectional PVCs.

Ventricular Tachycardia

Ventricular tachycardia is an infrequent manifestation of digitalis excess (10%) but has a high mortality of greater than 50%.[35] The rate is often faster than tachycardia precipitated by ischemia and may not be preceded by warning ventricular ectopy. Bidirectional tachycardia is considered pathognomonic of toxicity.[35,39] It occurs at a rate of 140 to 180 per minute and is recognized by a right bundle branch block morphology and alternating left and right axis deviation. The origin of the tachycardia may be atrioventricular or ventricular. The prognosis is grave with frequent evolution to ventricular fibrillation and sudden death.

Miscellaneous Dysrhythmias

Atrial fibrillation and flutter are uncommonly due to digitalis, especially if associated with a rapid ventricular response. Nonconducted (blocked) PACs are very suggestive of digitalis toxicity.[35] Frequent PACs may precipitate atrial fibrillation. Ventricular fibrillation is usually a preterminal event with a mortality of virtually 100%.

Digitalis Toxicity in Patients With Atrial Fibrillation

Patients in atrial fibrillation are often maintained on "toxic" doses and are thus susceptible to clinical toxicity. Clues to the diagnosis of digitalis toxicity in the presence of atrial fibrillation are as follows: slow ventricular response, complete AV block with junctional escape rhythm at a rate of 45 to 55 per minute, nonparoxysmal AV junctional tachycardia at a regular rate of 70 to 100 per minute, a tendency toward rhythm regularity, accelerated junctional rhythm with variable exit block resulting in a rapid irregular (or regularly irregular) rhythm and bidirectional tachycardia; all of above can occur without ventricular ectopy.[43] Of note is that the presence of a regular rhythm does not imply the presence of sinus rhythm, and the presence of irregular rhythm does not assure the presence of atrial fibrillation. Thus, electrocardiographic confirmation is necessary before altering therapy for atrial fibrillation.

Digitalis Toxicity in Patients With Pacemakers

The most important clue to toxicity is an altered atrial mechanism in the presence of an underlying pacemaker rhythm.[44] Independent retrograde P waves at a rate of 70 to 130 per minute suggest nonparoxysmal AV junctional tachy-

cardia; a rate of 40 to 60 per minute suggests AV junctional escape rhythm. Sinus bradycardia and sinoatrial block may be present. Atrial tachycardia is diagnosed by the recognition of independent upright P waves at a rate of 160 to 250 per minute. Premature ventricular complexes and ventricular tachycardia/fibrillation may also be present with an underlying pacemaker rhythm.

Therapy for Digitalis Intoxication

Therapy for digitalis toxicity is indicated for hemodynamically significant bradyarrhythmias or tachyarrhythmias, for arrhythmias with malignant potential and for hyperkalemia. Specific indications for treatment are ventricular ectopy (multiform, bigeminy, bidirectional), ventricular tachycardia (including bidirectional), ventricular fibrillation, atrial tachycardia with block, symptomatic bradyarrhythmias and nonparoxysmal junctional tachycardia at a rate of more than 90 per minute.

Therapy should begin with discontinuation of digoxin and diuretics (to replete potassium stores). The patient should be placed at bed rest to avoid sympathetic stimulation and exacerbation of digitalis arrhythmias. Monitoring is essential because multiple rhythms of variable hemodynamic significance may occur over time. Conservative therapy may be adequate for many of the digitalis dysrhythmias. The agents most useful in treating significant digitalis toxicity are reviewed below.

Potassium Chloride

Increasing extracellular potassium results in increased sodium-potassium pump activity and consequently decreased intracellular calcium and secondary afterdepolarizations. Potassium replacement is often the initial therapy of choice for ectopic rhythms (ventricular ectopy, ventricular tachycardia, atrial tachycardia with block and nonparoxysmal AV junctional tachycardia). It is contraindicated by renal failure, preexisting hyperkalemia and depressed AV conduction (greater than first-degree AV block). Hyperkalemia, by decreasing the resting membrane potential, can potentiate digoxin's effect on AV conduction.[34] The dose of potassium required to produce AV block, which is reduced in the presence of digoxin, however, is still more than the dose required to eliminate ectopic rhythms. A given dose of potassium chloride can produce a greater than expected increase in serum potassium levels due to inhibition of the sodium-potassium pump. Administering potassium chloride in glucose can paradoxically decrease serum potassium levels further by increasing intracellular potassium movement; administration in saline may be necessary.

Diphenylhydantoin

Given prophylactically, phenytoin is the best agent to retard the development of digitalis toxic dysrhythmias. Phenytoin appears to act in the central nervous system by depressing central sympathetic outflow. It suppresses digitalis-induced enhanced automaticity and delayed afterdepolarizations without reversing digitalis inotropism. It may also reverse digoxin-induced depression of AV and sinoatrial conduction.[12] Hypotension is the main adverse effect of intravenous administration of phenytoin. Phenytoin is administered by intravenous infusion at a rate of 100 mg every five minutes until the desired effect, toxicity or a total dose of 1,000 mg. This is followed by oral dosing of 400 to 600 mg per day until the toxicity is resolved.[12] There is often a critical dose at which arrhythmias are suppressed. Indications for phenytoin therapy are atrial tachycardia with block, ventricular ectopy, ventricular tachycardia and nonparoxysmal AV junctional tachycardia.

Lidocaine

In a manner similar to phenytoin, lidocaine suppresses digoxin-induced automaticity and delayed afterdepolarizations without depressing AV conduction.[12] In a patient with advanced AV block, however, suppressing the ectopic focus can precipitate ventricular standstill. Indications include ventricular ectopy or tachycardia and atrial tachycardia with block.

Magnesium

Intravenous administration of magnesium can suppress digitalis-induced ventricular arrhythmias in animals and in clinical use.[45] The use of magnesium is contraindicated in renal failure, hypermagnesemia and advanced AV block but is indicated for ventricular ectopy and tachycardia and perhaps for AV junctional tachycardia.

Atropine

Atropine is useful for reversing digoxin-induced AV and sinoatrial conduction delay. It is particularly effective in patients without underlying heart disease and with significant ingestion. Therapy is indicated for symptomatic bradyarrhythmias complicated by hypotension, angina, heart failure or bradycardia-dependent ventricular ectopy.

Isoproterenol

Indicated for temporary treatment of symptomatic bradycardias before pacemaker therapy, the use of isoproterenol can precipitate malignant ventricular ectopy, increase the amplitude of delayed afterdepolarizations and potentially worsen hypokalemia via a β_2-receptor effect.

Second-Line Antiarrhythmic Agents

Several antiarrhythmic agents have been relegated to second-line agents (Table 4) due to their potential for toxicity (worsened ventricular ectopy or AV conduction). Most are negative inotropes as well.

Treatment of Hyperkalemia

The treatment of hyperkalemia includes potassium exchange resins, glucose-insulin, bicarbonate, hemodialysis and antidigoxin Fab fragments. Calcium is relatively contraindicated because it can increase afterdepolarizations, and transient severe hypercalcemia sensitizes the myocardium to digoxin.

Carotid Sinus Massage

Digitalis sensitizes the heart to the vagal effect of carotid massage, and the maneuver in intoxicated patients can precipitate ventricular asystole, advanced AV block and malignant ventricular arrhythmias that are refractory to countershock.[46] There is no defined role for carotid massage as therapy for digitalis-toxic rhythms.

TABLE 4.—*Potential Uses and Toxicity of Second-Line Drugs for Digoxin Toxicity*

Drug	May Increase AV Block	May Increase Ventricular Ectopy	Negative Inotrope	Potential Indications
Procainamide hydrochloride or quinidine	Yes	No	Yes	Ventricular ectopy, ventricular tachycardia, atrial tachycardia with block, AVT
β-Blockers	Yes	No	Yes	Ventricular ectopy, ventricular tachycardia, atrial tachycardia with block
Verapamil	Yes	No	Yes	Atrial tachycardia with block, AVT, ventricular ectopy, ventricular tachycardia
Amiodarone	Yes	No	Yes	Ventricular tachycardia (refractory dysrhythmia)
Isoproterenol	No	Yes	No	Bradycardia (refractory dysrhythmia)
Bretylium tosylate	No	Yes	No	Ventricular tachycardia, ventricular fibrillation (refractory dysrhythmia)

AV = atrioventricular, AVT = nonparoxysmal atrioventricular junctional tachycardia

Pacemaker Therapy

Initiation of pacing is recommended for hemodynamically significant bradycardia refractory to atropine. Placement or displacement of a pacing catheter can precipitate ventricular arrhythmias in ventricles made "prefibrillatory" by the use of digitalis.[47] If AV conduction is intact, atrial pacing is preferable to minimize the risk of pacemaker-induced ventricular fibrillation. Overdrive pacing of triggered activity can result in "overdrive acceleration" of the underlying arrhythmia.

Cardioversion

Digitalis decreases the energy threshold for producing postcardioversion dysrhythmias by 2,000-fold.[48] Countershock can lead to refractory ventricular dysrhythmias. The extent of arrhythmias correlates with the energy level used and the level of digitalization. Postulated mechanisms for arrhythmias are the release of catecholamines from cardiac nerve endings and alteration of cardiac membranes leading to intracellular potassium egress. In patients (or animals) without overt evidence of toxicity, cardioversion does not precipitate arrhythmias.[49]

Recommendations include the use of the lowest effective energy setting and pretreatment with potassium chloride, phenytoin, lidocaine, quinidine or β-blockers. If β-blockers are administered to block catecholamine effect, atropine should be given to prevent postcardioversion asystole.

Dialysis (Renal, Gastrointestinal)

Hemodialysis, peritoneal dialysis and charcoal hemoperfusion are ineffective measures for reducing the total body digoxin content. Serial administration of activated charcoal by mouth may decrease the half-life of digoxin.

Immunologic Therapy for Digitalis Toxicity

About 20 years after the first report of the isolation of antidigoxin antibodies, an immunologic antidote has been established as the therapy for advanced, life-threatening digitalis toxicity. In 1966 Butler and Chen reported the initial isolation of antibodies to digoxin in rabbits.[50] Subsequently, sheep antidigoxin immunoglobulin (Ig) G molecules and Fab fragments were shown to reverse experimental digoxin-induced dysrhythmias, inotropism, inhibition of rubidium 86 transport and cellular electrophysiologic effects.[51,52] After the report of the first human case of reversal of life-threatening digoxin toxicity with Fab fragments in 1976, the experience in a multicenter trial has been extended to 63 patients.[53]

Table 5 outlines the mechanism of action of sheep antidigoxin antibodies.[54] Fab fragments have several advantages over intact IgG in that they have decreased immunogenicity due to loss of the Fc segment and smaller molecular weight leading to more rapid and effective distribution and reversal of toxicity. In addition, Fab-digoxin complexes are rapidly excreted by glomerular filtration, whereas IgG-digoxin is slowly degraded by the reticuloendothelial system. On intravenous infusion of Fab, intravascular and interstitial digoxin is bound, resulting in undetectable free (active) digoxin and more than a tenfold increase in total serum digoxin (bound plus free) content. A concentration gradient is thus created, leading to egress of intracellular digoxin. Fab fragments also bind digoxin molecules recently dissociated from receptor sites and prevent their reassociation because the affinity of digoxin is tenfold higher for Fab than for its receptor site. Reversal of digoxin toxicity is evident within one half to one hour. The excretion half-life of Fab-digoxin complexes is 16 to 20 hours. Antidigoxin Fab fragments are also useful for digitoxin even though their affinity for digitoxin is tenfold less.

For administering Fab fragments, the dose is calculated to be stoichiometrically equal to total body digoxin content. Calculations differ for acute and chronic ingestion and for digoxin and digitoxin use. The calculated dose of Fab is diluted in normal saline and, after confirmation of the absence of immediate hypersensitivity (serial skin testing, test intrave-

TABLE 5.—*Sequence of Reversal of Advanced Digoxin Toxicity by Digoxin-Specific Fab Antibody Fragments*

Sheep immunized with digoxin-serum albumin conjugate
IgG sheep antidigoxin antibody isolated
Antiserum digested with papain
Digoxin-specific Fab fragments purified, isolated
Fab administered intravenously to digoxin-intoxicated patient
Fab fragments bind intravascular digoxin, diffuse into interstitial space and find free interstitial digoxin
Decreased free (active) extracellular digoxin; increased bound (inactive) extracellular digoxin; significantly increased serum digoxin concentration by radioimmunoassay; undetectable free serum digoxin by equilibrium dialysis
Concentration gradient favoring egress of intracellular digoxin—subsequently bound by Fab fragments in extracellular space
Fab fragments bind freshly dissociated digoxin molecules and prevent their reassociation with membrane receptors
Reversal of adverse electrophysiologic effects of digoxin, usually seen within ½ to 1 hour of Fab administration; hyperkalemia rapidly reversed
Excretion of Fab-digoxin complexes by glomerular filtration with half-life of 16 to 20 hours

nous dose), is administered intravenously over 15 to 30 minutes.

The multicenter trial of Fab therapy reported by Wenger and co-workers showed resolution of advanced toxicity in 52 of 56 analyzed patients.[53] Of the 63 studied patients, 33 had accidental or suicidal overdose. No response was seen in three patients, but the diagnosis of digitalis excess was uncertain in these cases. In all, 52 patients had complete resolution of toxicity. A response to Fab infusion was usually seen within 30 minutes. Based on this experience, current indications for Fab therapy include acute, massive digitalis overdose, life-threatening arrhythmias or conduction deficits unresponsive to conventional therapy and refractory hyperkalemia. In the multicenter trial, no correlation was found between the level of hyperkalemia and outcome, implying a significant impact of Fab on mortality.

Theoretical concerns about infusion of heterologous antibodies have not materialized. No patient in the multicenter trial had an adverse hypersensitivity response.[53] The following concerns, however, remain:

- An anamnestic immune response with repeat Fab administration.
- Dissociation of digoxin from Fab-digoxin complexes with recrudescence of toxicity in patients with a prolonged elimination half-life of Fab-digoxin—that is, in cases of renal failure; no recrudescence has been seen to date in patients with a decreased glomerular filtration rate.
- Reversal of digoxin inotropic response may be detrimental in patients with compromised ventricular function, but additional digoxin can restore the inotropic effect.
- Possible delayed serum sickness.

To circumvent the difficulty of preparing large quantities of Fab fragments from many sheep and to improve standardization, a somatic cell fusion technique has been developed to produce "in vitro" monoclonal antibodies to digoxin. Lechat and associates showed the efficacy of monoclonal IgG and Fab fragments in reversing toxicity in guinea pigs.[55] Monoclonal IgG fully reversed toxicity in six of eight animals. Monoclonal Fab fragments, however, more rapidly reversed toxicity in all ten animals so treated. No clinical experience has been reported, but the potential of such therapy is obviously of tremendous academic and practical value.

Conclusion

Withering's cautions about the potential toxicity of digitalis remain as pertinent today as when first published in 1785. The incidence of toxic reactions remains high, affecting almost one of every five patients treated with digitalis glycosides. Physician education has contributed to a decline in the incidence of toxicity, but the mortality of unrecognized toxicity remains high. Several therapies are available for the diverse dysrhythmias induced by digoxin. Immunologic therapy, when widely available, will have a significant impact on the mortality due to digitalis toxicity. Therapy will be effective, however, only if toxicity is first recognized. In conclusion, in 1986 we have realized Withering's dream of an effective digitalis antidote, and we can see more light; yet, due to a lack of rapid recognition of intoxication, there is still more tunnel ahead.

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Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Contralateral Breast Surgery Following Mastectomy

QUESTION:

Following mastectomy with breast reconstruction, is a surgical procedure on a disease-free, contralateral breast to attain symmetry considered accepted medical practice?

If so, is it considered a cosmetic procedure?

OPINION:

In the opinion of the Scientific Advisory Panels on General Surgery and Plastic Surgery, reconstruction of a disease-free contralateral breast to restore symmetry is considered established medical practice following mastectomy with breast reconstruction. This reflects the commonly accepted goals of breast reconstruction which are to provide a contour as natural looking and feeling as possible, to create a natural looking nipple/areola complex and to obtain acceptable symmetry with the opposite breast.

When the contralateral breast is excessively large, in size or volume, or droops severely (ptosis), it is usually impossible to match these characteristics with the newly reconstructed breast. To restore symmetry, therefore, reduction mammoplasty of a large breast, mastopexy of a drooping breast and augmentation mammoplasty of an unusually small breast may be necessary. Patients with a high risk of cancer developing in the contralateral breast who need size or shape correction to achieve symmetry may be considered for mastectomy and immediate reconstruction.

Because the breasts are paired organs and symmetry is the natural state, contralateral breast reconstruction is considered a restoration of the normal condition. In this sense, the procedure is reconstructive, not cosmetic.

For the psychological well-being and physical appearance and functioning of many women, breast reconstruction following mastectomy is essential. Contralateral breast reconstruction is understood to be an integral part of this surgical care.

Epitomes

Important Advances in Clinical Medicine

Neurosurgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in neurosurgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in neurosurgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Neurosurgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Early Versus Delayed Operation in Subarachnoid Hemorrhage

SUBARACHNOID HEMORRHAGE from a ruptured intracranial berry aneurysm remains a major source of morbidity and mortality in adults, afflicting patients in their most productive years. Many die before reaching a hospital, while others succumb to rebleeding and vasospasm after their original hemorrhage.

Rebleeding is most frequent in the first three weeks following aneurysmal rupture—its peak being at day 1—and kills and disables an additional 17% of patients reaching referral centers. Symptomatic cerebral vasospasm occurs in about a third of the patients between day 3 and day 21 and causes severe stroke or death in half of these. Traditionally, definitive surgical treatment (clipping of the aneurysm) has been delayed to avoid inducing or aggravating vasospasm in the acute state and to allow the cerebral swelling that follows the initial rupture to resolve. Because patients die while awaiting an operation, however, there has been recent interest in earlier operative intervention. Early surgical intervention effectively decreases the incidence of rebleeding and allows a more aggressive medical management of vasospasm using hypertension and hypervolemia without the risk of another rupture. It also allows the removal of spasmogenic clot from the basal cisterns, and it reduces medical complications related to prolonged bed rest and antifibrinolytic therapy.

A recently completed cooperative study addressed the problem of management morbidity and mortality with early versus delayed surgical treatment. Preliminary findings suggest that an early operation may improve overall outcome in most patients. In good grade patients, the surgical mortality does not significantly change if an operation is done early. Clearly, more patients die while waiting for a delayed surgical procedure than die as a result of increased risks of an early one. Furthermore, early operation does not increase the incidence or worsen the outcome of symptomatic vasospasm. Only patients with severe clinical vasospasm at the time of presentation appear to benefit from cautious delay of the operation until symptoms have cleared.

It is foreseeable that an increased awareness of this entity in the general population will lead to a much earlier recognition of the disease through its warning symptom—that is, sentinel leak—and early surgical repair can be carried out before the devastating effects of major aneurysmal rupture occur.

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Chronic Benign Pain Management

CHRONIC BENIGN PAIN is estimated to affect as many as 20 million people in the United States, representing an enormous loss of productivity, large medical expenses and considerable suffering for the persons so affected. A multidisciplinary team approach to pain management emphasizes an accurate initial diagnosis and treatment directed at reducing drug dependence and increasing functional capabilities. Techniques used include behavioral modification, physical therapy, transcutaneous electrical stimulation, nerve blocks, hypnosis, biofeedback and acupuncture, among others.

In general, neurosurgical therapy for chronic benign pain should be used only after a thorough trial of treatment by a multidisciplinary pain management team. Two recent neurosurgical procedures for treating chronic benign pain include electrically stimulating deep brain structures and placing lesions in the dorsal root entry zone of the spinal cord. The brain stimulation technique is based on results of studies in animals that showed powerful pain inhibitory pathways descending from the periaqueductal grey region of the brain stem and

from the thalamus to the dorsal horn region of the spinal eord. In the animal studies, analgesia from periaqueductal stimulation appeared to be related to release of naturally occurring opiatelike substances, the so-called endorphins. The neurotransmitters involved in pain relief for lateral thalamic stimulation are unknown. To treat chronic pain in humans, these pain-inhibiting systems may be electrically activated by stereotactic placement of stimulation electrodes in either brain site. Pain may be relieved in 65% to 70% of patients by the brain-stimulating technique, with few complications and without interference with normal neurologic function. Excellent results have been obtained in patients with chronic back and leg pain after unsuccessful spinal operations. Good results have also been obtained in patients with chronic pain due to trauma, postherpetic neuralgia, anesthesia dolorosa and certain nerve entry injuries.

The technique of placing lesions in the dorsal root entry zone is based on studies that showed neuronal hyperactivity in the dorsal horn of the spinal cord following deafferentation. Made by either a radio-frequency electrode technique or with a laser, these lesions have relieved chronic pain in a high percentage of patients following spinal cord injury and avulsion of the brachial or lumbar nerve plexuses. Because this technique is used for treating pain following deafferentation, pain relief may be accomplished without further loss of neurologic function.

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Intraoperative Monitoring With Ultrasonography

VARIOUS METHODS have been used in the past to locate intraoperatively lesions of the central nervous system. These techniques have usually required that the neurosurgeon transfer static information from diagnostic imaging studies to the operative situation. By applying ultrasonography to neurosurgical procedures, it has become possible to utilize data as it is generated (real-time) in localizing lesions.

The usual method of scanning for intracranial lesions is to first scan transdurally with a low-frequency transducer. In this way, the operator may become oriented by identifying structures such as the ventricles and the falx cerebri. Once the dura is opened, the lesion may be further characterized by using transducers that provide higher resolution. When scanning the intraspinal contents, the surgical wound is filled with sterile saline that serves as a coupling agent. Using a high-frequency transducer, scanning is carried out in a systematic manner noting the position of structures such as the central canal. Using the scanner's computer, the depth and the size of intracranial and intraspinal lesions may be determined.

Intraoperative ultrasonography enables a surgeon to readily identify lesions with high echogenicity, such as solid tumors, hematomas, displaced bone and missile fragments, and those with low echogenicity, such as abscesses, syringomyelic cysts and enlarged ventricles. Excision, aspiration, biopsy or cannulation may then be done and monitored under ultrasonic control.

Except in infants with an open anterior fontanelle, an opening in the intaet calvarium or the spine must be created to accommodate the ultrasonic probe. As intraoperative ultrasonography continues to be widely used in neurosurgieal procedures, it is anticipated technology will provide probes requiring smaller bone openings.

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Diagnosis and Surgical Management of Cervical Syringomyelia

CERVICAL SYRINGOMYELIA is a cystic dilation that develops in the cervical spinal cord, typically originating in the region of the vestigial central canal. Clinically, syringomyelia produces pain and progressive sensory loss to pain and temperature modalities in the upper extremities and upper cervical-thoracic region and with time can lead to a complete loss of spinal cord funetion below the lesion. The natural history of syringomyelia is highly variable. While some patients' conditions improve or stabilize without surgical therapy, others deteriorate even with the most aggressive intervention. While the cause of cervical syringomyelia is unclear, it commonly develops in patients with the cerebellomedullary malformation syndrome (Arnold-Chiari syndrome) with obstruction of the outlet foramina of the fourth ventricle. In some cases, no causative factors can be identified. Posttraumatic syringomyelia can develop in patients with spinal cord injury, typically in those with complete traumatic spinal cord transection in the thoraeic region. In these cases, indolent progressive loss of sensory and motor function above the level of spinal cord transection may indicate the development of a syrinx. Occasionally intramedullary spinal cord tumors can also be associated with cystic accumulations of fluid within the spinal cord that can mimic the syndrome of syringomyelia.

The neuroradiologic diagnosis of syringomyelia has been greatly facilitated by the development of magnetic resonance (MR) imaging, in that MR imaging provides a complete visualization in the sagittal plane of the cervical cord, craniocervical junction and related regions. Also, associated hydrocephalus, cerebellar tonsillar and posterior fossa abnormalities can be visualized with their relationship to the cervical spinal cord. Operative strategies may be planned based on the MR imaging data. In addition, its use avoids invasive procedures such as myelography or cisternography and it can be done on an outpatient basis.

A large number of operations have been advocated for treating syringomyelia, including posterior fossa decompression with or without plugging of the communication of the

fourth ventricle with the central canal of the spinal cord, syringostomy with syringosubarachnoid shunting, terminal ventriculostomy, ventriculoperitoneal or ventriculoatrial shunting and syringoperitoneal shunting. The choice of procedure is based on the suspected cause of the syringomyelia and the anatomic data obtained by MR imaging.

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Surgical Therapy for Medically Intractable Epilepsy in Children

THE RENEWAL OF INTEREST in the surgical treatment of medically intractable epilepsy is well illustrated by the occurrence of two international conferences devoted to the subject in the past six months, after more than a dozen years without one. This renewed interest extends to the use of surgical approaches in children with difficult seizure problems. Cortical resection is the surgical approach most likely to completely control seizures. The indications for cortical resection in children in their early teens (and perhaps even younger) are the same as for adults: medical intractability, the presence of a focus of seizure onset and evidence that the focus is not in a brain area essential for motor, speech or memory function. Most of these patients will have temporal lobe epileptic foci. Medical intractability means a persistence of seizures after trials of the major antiepileptic drugs at therapeutic serum concentrations: phenytoin and carbamazepine alone and together for complex partial seizures of temporal lobe origin. Most patients who achieve seizure control on antiepileptic drug therapy do so within six months of reaching therapeutic drug concentrations. Children in their early teens with partial complex temporal lobe seizures seldom outgrow them; waiting for this to occur, therefore, is not a reason to defer surgical treatment. The more satisfactory rehabilitation that follows seizure control in the teens rather than the 20s is a reason to consider earlier surgical intervention.

Papers given at recent conferences indicated that no one diagnostic approach is suitable to identify a focus in all patients. In one subset of candidates who are particularly likely to have their seizures controlled by a surgical resection, the focus can be identified by noninvasive means without the use of depth electrodes or other techniques of ongoing direct brain recording. The exact noninvasive criteria used by various centers differ but often include localized interictal epileptiform abnormalities on scalp electroencephalography (EEG), evidence of fast motor responses and a lack of psychopathology on neuropsychological testing or measures of focal functional deficit, especially evidence of localized glucose hypometabolism on positron emission tomography. On the other hand, ongoing direct brain recording techniques have been of value in other patients who do not meet these noninvasive criteria due to bilateral, especially bitemporal, epileptiform abnormalities. In a large proportion of those patients, direct brain recording, coupled with intensive video and EEG monitoring, has shown that most or all major, socially disabling seizures arise from one temporal lobe. Surgical resection of that temporal lobe has a reasonable chance of controlling major seizures. A wide variety of ongoing direct brain recording techniques are currently in use, including stereotaxically implanted depth electrodes, subdural strips and tubes and subdural or epidural plates of electrodes. The advantages of each approach are still being determined.

The hemisphere containing the epileptic focus for language and memory is usually determined preoperatively by intracarotid perfusion of amobarbital (Wada test), a procedure that can be used in children as young as 6 years. If the focus is in the dominant hemisphere, the areas essential for language are localized by electrical stimulation mapping and these areas spared in the resection. The intraoperative use of this approach, however, requires the use of local anesthesia that children in the early teens, and perhaps younger, will tolerate. The use of epidural or subdural plates of electrodes provides an alternative technique to obtain the same localization information in children who cannot tolerate a procedure under local anesthesia. Resections can also be carried out in a temporal lobe essential for memory, but this requires sparing both hippocampus and lateral temporal memory areas as identified by electrical stimulation mapping. With the use of these techniques, the risk to language and memory is sufficiently low that having the epileptic focus in the dominant hemisphere is not a reason for deferring resection.

The decision to undertake a surgical resection should be made based on the impact to a child of the control of seizures alone. Behavioral problems do not reliably improve after an operation for seizure control, and this goal is not by itself an indication for surgical therapy for seizures.

Surgical therapy may also be of value in several special situations. In very young children, surgical therapy is usually reserved for intractable seizures with a clear focal onset; a substantial number of these children will have the distinctive pathologic changes of Rasmussen's encephalitis. Children with the infantile hemiplegia syndrome have a high probability of seizure control after hemispherectomy. Recent modifications in the technique of this operation seem to have reduced the long-term complication of bleeding into the resection site and the subsequent development of a communicating hydrocephalus. The value of sectioning the corpus callosum in the treatment of seizures is still being debated. There is a developing consensus, however, that it may have some value in patients with frequent major motor convulsive (grand mal) seizures without a focus and in frequent drop seizures where the patient is likely to sustain injury.

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Chemotherapy in Conjunction With Blood-Brain Barrier Modification in Patients With Cerebral Metastasis

ONE OF THE MAJOR PHENOMENA responsible for the failure of chemotherapy in the treatment of central nervous system (CNS) tumors may be the unique anatomic aspect of the blood-brain barrier. This structural barrier, composed of tight junctions between CNS capillary endothelial cells, serves primarily a protective regulatory function constraining diffusion across capillaries in relation to lipid solubility and molecular weight. Whereas it was formerly suggested that there was no effective barrier to drug delivery in CNS tumors, more recent studies indicate that considerable variations in barrier integrity exist between tumors, within the same tumor and particularly at the actively proliferating edge of a tumor. The clinical expression of the barrier is exemplified by the reports of increasing size of brain metastases when other extraneural parenchymal sites of tumor invasion regressed due to systemic chemotherapy.

The extent to which the blood-brain barrier limits drug delivery to CNS tumors remains an area of controversy and extensive investigation. Expansion of our studies in animals provided the basis for clinical trials, and we are presently evaluating clinical efficacy in a Phase II trial using combination chemotherapy (methotrexate sodium given intra-arterially and leucovorin calcium rescue by mouth, cyclophosphamide given intravenously and procarbazine given orally) in patients with glioblastoma, CNS metastasis and CNS lymphoma. To date, 89 patients have received combination chemotherapy in conjunction with blood-brain barrier modification in 590 procedures.

In our small pilot series of seven patients with CNS metastasis (from breast, lung or testicle), three observations are of note. In one patient, a metastatic lesion was evident on enhanced computed tomographic (CT) scan only after osmotic barrier modification, supporting the existence of a completely intact blood-brain barrier in the tumor. Second, in another patient there was radiographic documentation of tumor regression in those areas of the brain infused while tumor progressed in portions of the brain distant from the areas of barrier opening. Third, the increased delivery of chemotherapeutic agents associated with barrier modification may be of benefit even in those patients who have undergone surgical and radiation therapy and systemic chemotherapy.

We have observed the following complications in our overall series of 89 patients: infarcts (3%), transient exacerbation of preexisting neurologic deficits—presumably due to an increase in brain water secondary to blood-brain barrier modification—(50%), seizures (15%) and readmission to hospital when patients have fever and granulocytopenia (33%). The significance of these studies relates directly to the grave prognosis associated with cerebral metastasis. Drug delivery is a major factor in treatment and reversible osmotic blood-brain barrier modification is likely to enhance the delivery of cytoreductive agents with minimal toxicity.

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Stereotactic Interstitial Irradiation (Brachytherapy) of Malignant Gliomas

BRACHYTHERAPY involves implanting radioactive sources directly into a tissue to deliver a calculated dose of radiation to a specific volume of that tissue. The technique has special appeal in neuro-oncology. The doses that have been delivered to the periphery of a brain tumor by brachytherapy are in the range of 3,000 to 12,000 rads compared with about 6,000 rads for standard teletherapy. The radiation dose delivered by combined brachytherapy and teletherapy may be substantial for the treatment of malignant gliomas.

Three factors have provided the impetus for an aggressive reevaluation of brachytherapy in managing malignant gliomas. The evolution of computed tomographic (CT) imaging technology has been combined with CT-scan-compatible stereotactic equipment and with improved computerized planning of radiation therapy. Current practice requires a confirmatory stereotaetic biopsy of the lesion followed by placement of catheters into the tumor in locations selected on the basis of computer-generated isodose curves that precisely encompass the area on CT scan. The final array of the radioactive sources are afterloaded into the catheters. The sources are left in place until the calculated total dose has been delivered at a dose rate of 20 to 100 rads per hour. The dose rate depends on the specific activity of the isotope, the number of radioactive sources and their geometric distribution. The isotope ribbons and catheters are removed at the bedside on completing the radiotherapy plan.

The treated area undergoes radionecrosis and the fate of this damaged tissue is critical to the success, failure and complications of the therapy. If this technique is to be curative, the tumor under treatment must be localized and completely contained within the isodose curves that provide a dose sufficient to destroy the tumor. If these criteria are not met, then the treatment is palliative at best. In some patients, a delayed radionecrosis in the tumor volume can be progressively harmful by producing intractable cerebral edema. The experience of Gutin and Leibel with high-energy iodine 125 sources has resulted in a need for a craniotomy to remove a radionecrotic mass in about 30% of patients after implantation. Many of these patients, however, will have excellent long-term control of their disease, and the duration of survival achieved with recurrent malignant gliomas is superior to the best chemotherapeutic trials. The quality of prolonged life, however, has yet to be satisfactorily reported.

Many factors have to be studied before brachytherapy is recommended as standard therapy for malignant glioma. What role might the magnetic resonance imaging sean have in selecting focal versus diffuse gliomas? What is the best radiologic technique to define the "living" perimeter of the tumor? Should the treatment be restricted to recurrent disease or might it supplement teletherapy at some unknown ideal interval after completion of initial treatment and in relation to an unknown schedule of chemotherapy and radiosensitizers? What isotope is best? What is the ideal dose-rate and total dose

of radiation to the tumor periphery? What is the ideal number of catheters to produce a homogeneous distribution of radiation? Is the frequency of symptomatic radionecrosis less with a particular technique of radiodosimetry? Are there anatomic sites of tumor or tumor geometries that are ideal for or that contraindicate brachytherapy?

The technology and equipment required to do brachytherapy are now commonplace. Until these questions are answered in authoritative studies, however, brachytherapy remains a therapy under review.

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Intrauterine Surgical Procedures and the Management of Hydrocephalic Fetuses

BEFORE THE EARLY 1960s, experience with human fetal operations was nonexistent. Ten years later, refinements were being made with ultrasonography that led to unprecedented images of the fetal anatomy. With current technical advances, high-resolution, real-time ultrasonography can portray excellent detail of the entire fetus and, in particular, the developing nervous system. At 9 and 12 weeks of gestational age, the fetal skull and lateral ventricles, respectively, can be recognized. Although fetal hydrocephalus has become easy to identify during the third trimester, earlier detection of ventricular enlargement—that is, during the second trimester—continues to pose a difficult management problem.

Experience with animal models of fetal hydrocephalus seemed to indicate that in utero diversion of cerebrospinal fluid to the amniotic cavity was beneficial in reducing the adverse effects of hydrocephalus, such as ependymal destruction, periventricular gliosis and loss of the cortical mantle. Several reports have now been published describing the placement of ventriculoamniotic shunts into hydrocephalic human fetuses. Although ventricular decompression was achieved in most of the reported cases, technical problems such as shunt migration and malfunction were not insignificant. Perhaps the most important observation in this group was the associated anatomic defects involving the central nervous system (CNS). Highly skilled ultrasonographers using the most advanced equipment may fail to recognize these associated defects. Thus, false expectations regarding survival and future outlook based on sonographic data may lead to inappropriate in utero intervention.

Tantamount to the recognition of these associated anomalies is understanding the natural history of fetal hydrocephalus. In a retrospective analysis of 24 cases with fetal ventriculomegaly followed to term, Glick and colleagues identified 11 fetuses that had isolated ventricular enlargement without associated life-threatening anomalies. Of the 11 fetuses, 10 showed stable ventricular size throughout gestation; only one fetus showed a progressive increase in the size of the ventricles. Three newborns required a shunt due to increased intracranial pressure. Additional CNS malformations were recognized in three cases soon after birth, however, which again points out the limitations of fetal ultrasonography. In addition, 80% of those infants requiring ventricular shunt procedures developed normally, emphasizing the unlikeliness of improving outcome with an intrauterine ventriculoamniotic shunt.

Most neurosurgeons have now placed a moratorium on the in utero treatment of fetal hydrocephalus. The high incidence of concomitant congenital anomalies associated with fetal ventriculomegaly, a better understanding of the natural history of this entity and a lack of adequate time for follow-up on those infants who undergo intrauterine shunt insertion justifies this prenatal policy of nonintervention. A fetus in the midtrimester that is normal by routine screening methods but showing progressive ventricular enlargement and no other recognizable defects represents a challenging therapeutic dilemma. If pulmonary maturity can be verified or induced with steroids, delivery should be carried out and a shunt placed. If the viability of the fetus is questionable, however, a conservative approach seems indicated until maturity develops and warrants preterm delivery.

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AIDS and the Nervous System

EPIDEMIOLOGIC STUDIES have shown that fully 39% of patients with the acquired immunodeficiency syndrome (AIDS) have significant neurologic complaints, and neurologic symptoms led to the initial diagnosis in 10% of all patients with AIDS. These patients most frequently present with progressive dementia, although seizures and focal neurologic deficits are common. Computed tomographic (CT) brain scans are normal in 41% of these patients and show diffuse cerebral atrophy in 38% and space-occupying lesions in 22%. Those patients with atrophy on CT scans appear to be at a higher risk of neurologic progression than those with normal CT scans. Recent studies indicate that magnetic resonance (MR) imaging is much more sensitive than CT for showing intracranial pathology in a patient with neurological symptoms, and thus MR imaging is now the neuroimaging procedure of choice in the screening of these patients.

The most common neurologic syndrome in a patient with AIDS is subacute encephalitis; this progressive, invariably fatal, dementing illness probably results from primary infection of the brain with human T-cell lymphotropic virus type III, the virus presumed to cause AIDS. The other most frequent neuropathologic processes included cryptococcal meningitis, *Toxoplasma gondii* encephalitis or abscess or both and primary central nervous system (CNS) lymphoma. There have been several reports of multiple coexisting intracranial pathologic conditions developing in AIDS patients.

Current recommendations for the evaluation of a patient with AIDS who has CNS symptoms include initial screening with MR imaging. If a space-occupying lesion is identified

and the patient is neurologically stable, an empiric trial of antitoxoplasma therapy is instituted. If the patient is neurologically unstable, harboring a large mass lesion with risk of herniation or fails to respond to a three-week trial for presumed toxoplasmosis, biopsy is indicated. As several intracranial pathologic conditions may exist, repeat biopsy of lesions that progress despite specific therapy may be indicated to identify other treatable processes. In those patients without lesions on MR imaging, lumbar puncture should be done and treatment initiated on the basis of the cerebrospinal fluid findings. Those patients with normal neuroradiologic and cerebrospinal fluid findings warrant close clinical follow-up and repeat studies at regular intervals or at the time of neurologic progression.

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Ultrasonographic Evaluation of Carotid Artery Disease

NONINVASIVE SCREENING TESTS of the carotid bifurcation, which aid in selecting patients for carotid arteriography, help avoid the morbidity and cost of that procedure and provide for safe serial examination of carotid disease. The two most widely accepted, increasingly available and reasonably accurate tests are duplex ultrasonography or scanning and digital intravenous angiography. Duplex scanning combines a B-mode, range-gated, short pulse ultrasound beam producing a high-resolution, real-time image of the vessel with a spectrum analysis display of the blood flow frequencies and amplitudes at that locus.

Both digital intravenous angiography and duplex scanning are highly sensitive for detecting stenotic lesions of 50% or more, with neither test being clearly superior. Digital subtraction angiography tends to underestimate disease severity in 72% of cases, whereas duplex scanning tends to overestimate 64% of the time. Duplex scanning is excellent for visualizing the "soft plaque," but its specificity for ruling out any degree of disease is only 20%. Spectral analysis improves considerably the accuracy of the B-mode image by detecting minimal and calcium-covered lesions usually overlooked by the latter. In several studies of stenosis alone, duplex scan sensitivity ranged from 90% to 95%, specificity 87% to 96% and accuracy 86% to 95%. Results of ultrasound studies agreed with those of a conventional angiogram absolutely in 71%, well in 20% and poorly in 9%.

Besides requiring a skilled technician, duplex scanning presents other disadvantages such as difficulty in differentiating a tight stenosis from a total occlusion and in identifying ulcerations.

Indications for duplex ultrasonography include an asymptomatic bruit, syncopal episodes, vague neurologic symptoms that might represent stroke, serial assessment of carotid lesions, detecting recurrent stenosis in patients following carotid endarterectomy and screening of patients scheduled for hypotensive anesthesia. It has recently been used intraoperatively to detect flaws in carotid reconstruction. Patients with typical carotid disease symptoms of amaurosis fugax, hemispheric stroke or transient attacks are better studied by conventional biplane arteriography because the likelihood of surgical or aggressive medical treatment is high. Ultrasonography does not delineate the aortic arch vessels, the cervical carotids cephalad to the mandible or the intracranial vessels.

The use of noninvasive testing such as duplex scanning results in a higher yield at cerebral angiography in patients with severe carotid occlusive disease. Nevertheless, the conventional biplane arteriogram at present is still the gold standard for analyzing carotid artery disease, and the final decision to proceed with it must still be based on clinical judgment.

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Cranial Neuropathies

MICROVASCULAR IMPINGEMENT on certain cranial nerves as they traverse the subarachnoid space of the posterior cranial fossa appears to be related (perhaps even causally) to the development of specific sensorimotor syndromes. Cross-compression of these neural structures may produce a focus of hyperexcitability that is manifest in a clinical syndrome relevant to the area mediated by the particular cranial nerve. In the case of the fifth or trigeminal nerve, the syndrome produced is trigeminal neuralgia. In this disorder, patients typically experience unilateral, lancinating, electric shock-like facial pain. If the seventh (facial) nerve is involved, unilateral, paroxysmal facial twitching, which often begins in the region of the orbicularis oculi, termed hemifacial spasm, is the result. Vascular distortion of the glossopharyngeal (ninth) and vagus (tenth) nerves can lead to glossopharyngeal neuralgia. In this syndrome, pain occurs in the pharyngeal region that resembles that of trigeminal neuralgia in its temporal pattern and lancinating quality. Other syndromes purported to result from microvascular compression of the acoustic (eighth) or the spinal accessory (eleventh) nerves have been described but have not yet been as widely accepted.

Although most cases of trigeminal neuralgia respond, at least initially, to carbamazepine therapy, hemifacial spasm and glossopharyngeal neuralgia respond poorly to this and other medical therapy. If the diagnosis can be made and the particular syndrome is refractory to medical management, these patients are candidates for microsurgical decompression of the involved cranial nerve. This is done under general anesthesia via a posterior fossa craniectomy. The cranial nerve is visualized with the aid of an operating microscope, the offending vessel is carefully moved from its point of contact with the nerve and a small piece of teflon felt is interposed between vessel and nerve.

Success with this surgical approach depends on the partic-

ular cranial nerve decompressed. In cases of trigeminal neuralgia, an initial success rate of up to 97% and a long-term rate of 80% can be anticipated. Both hemifacial spasm and glossopharyngeal neuralgia are eliminated in about 80% of patients after microvascular decompression of the respective cranial nerves. These procedures have been carried out now for more than a decade and long-term follow-up indicates these impressive results have persisted.

Clinical and laboratory research efforts have neither yielded the mechanism of these cranial neuropathies, nor have they precisely determined what role the microvascular cross-compression plays. Further questions remain as to why certain nerves seem prone to the development of a clinical syndrome, while others are minimally so. Future investigative efforts may clarify whether other disorders stem from vascular compression of neural structures in the posterior fossa. Nevertheless, microvascular decompression offers an important method of treatment in a growing number of cranial nerve syndromes.

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Magnetic Resonance Imaging

OVER THE PAST TWO YEARS, in a dramatic technologic advancement, magnetic resonance (MR) imaging has assumed an important role in neurodiagnosis. Although computed tomographic (CT) scanning is still the better technique for assessing most acute cranial or spinal disorders involving hemorrhage or trauma, MR imaging has proved capable of visualizing a variety of central nervous system lesions that in some instances cannot be seen on CT. Remarkable images of such lesions, including multiple brain lesions seen at times in multiple sclerosis, the acquired immunodeficiency syndrome, brain abscesses and metastatic tumors, have been obtained.

Because MR imaging is extremely sensitive to changes in the brain water content, lesions associated with brain edema—the gliomas, meningiomas and intracerebral hematomas, among others—are readily visualized. Bone does not show up well on MR images, and so this technique is particularly valuable in assessing posterior fossa lesions, such as brain-stem gliomas, acoustic nerve sheath tumors and infarction—conditions for which CT is at a disadvantage because of bone artifact or because many of these lesions are nearly isodense with brain on CT. Conversely, MR imaging is not as consistently useful as CT scanning in evaluating bone abnormalities unless the bone lesion is caused by tumor involvement.

MR imaging has rapidly been accepted as the superior diagnostic test for many spinal cord and spinal canal abnormalities. Cord or dural sac compression is seen readily on MR images. Nerve root compression by a herniated intervertebral disc, though, may still be best evaluated by CT or myelography. Spinal cord tumors and syrinxes can be defined well on MR images, whereas they may not be seen at all on other studies. With conventional or CT myelography, their presence often can only be inferred by cord widening. Conventional myelography soon may be used only rarely, in view of the minute detail displayed by MR imaging and the improvement in CT spine images that has been obtained.

Because MR imaging is generally more sensitive than CT in detailing brain and spinal cord lesions, it is in many cases, wherever available, the procedure of choice for an initial diagnostic study. The exceptions are patients with acute trauma, stroke or suspected intracranial hemorrhage, in which cases CT scanning without contrast is indicated. Caution is necessary in scanning patients who may have metallic implants. The cost of CT scans and MR imaging of the spine and brain is comparable. Recognizing the value of MR imaging, the State of California's Medicaid program (Medi-Cal) now provides reimbursement for MR imaging done to evaluate brain and spinal cord pathology. The safety, efficacy and sensitivity of MR imaging have established its position as a critical diagnostic tool for neurologic disease.

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Editorials

Troublesome Trends

If one looks upon our society as a kind of living organism, which in many ways it is, one can be troubled by a number of things we are doing both to and for our societal health. The long-term health and well-being of any species or society, or nation for that matter, depend more on the health of its young than on that of its elderly. Looked on in this way, are we protecting our elderly at the expense of our youth? Put another way, are we rewarding the past at the expense of preparing for the future? And what has been and should be the part played by medicine and the medical profession? In this view there appear to be some troublesome trends in this nation in health, education and the allocation of resources.

Profound changes are occurring in the demography of our population. The proportion of elderly is increasing and most of these people are white. The numbers of the young are also increasing, particularly among the nonwhite population. It is expected that in California, for example, soon after the turn of the century the whites in the population will be in a minority. It is known that the health status of many of these nonwhite minorities is below that of the population as a whole, and many more of them are educationally disadvantaged. These trends are disturbing if indeed our society can be compared to a living organism or species that seeks fitness for survival. These trends are equally disturbing if society is viewed as an economic organism in a tough world of economic competition with other nations, too many of which have already achieved higher rates of literacy, for example, than have we.

When one looks at how we as a nation allocate some of our resources, one senses that rewarding the past is a higher priority than preparing for a healthy biologic and economic future. Social Security payments to the elderly are sacrosanct whether they are needed or not, and in the private sector the elderly can receive many goods and services at reduced cost just because they are senior citizens. In health care it is clear that, for whatever reason, the elderly use a disproportionate share of the resources, much of this at public expense. At both ends of the life span, public espousal of the right to life results in enormous expense for sophisticated care when there is little expectation there will be any quality or usefulness for a life that is saved or prolonged. And at the same time it has been difficult and often impossible to find adequate resources to improve the health of the young. Similarly difficult to find have been resources to improve the quality of the school systems in which the young should be educated, not only to be literate but also to compete effectively as persons and as a nation in a highly technologic and increasingly interdependent world. And one can only wonder how much the fact that the elderly vote, and the young cannot, has had to do with the allocation of resources for health and education. But this seems to be the way our democratic system is working.

Now, what has been and what ought to be the responsibility of medicine in all of this? Medical science and technology have contributed enormously to the changing demography. They have contributed substantially to survival among both the young and the elderly. But in the general population, health has not improved as much with modern health care as was expected, and this disappointment has resulted in something of a backlash against the profession. It cannot be gainsaid, however, that medicine and medical technology, or the lack of them, have been a principal cause of many of the troublesome trends we see developing, especially if we view our society as a biologic or economic organism competing for health and survival.

One may reasonably ask, is there a flaw in our democratic system that seems to favor the elderly who are its past, at the expense of the young who are its future? And is there a flaw in our health care system that emphasizes high-tech patient care even when there is little to be salvaged, while cutting back on needed health care for minority and other groups who have higher rates of illness and mortality, and whose young are going to be an increasing portion of the population? And is there a profession that can understand the analogy of a human society to a biologic system, and call attention to what can only be a real challenge to our democratic system, our educational system and our health care system if we as a nation are to continue to be competitive in the world of tomorrow?

There is a glimmer of hope. It comes not so much from the medical profession as from patients and the people themselves. There is a recent and apparently growing emphasis on mental and physical fitness. But this is only a tiny beginning of what must be done if we are to assure that our society is to be a biologically healthy and economically effective organism, well prepared for health and survival in what may be a fiercely competitive future. The troublesome trends should be recognized for what they forecast for our society and our nation. Aware or not, the medical profession is positioned to play an important and leading role.

MSMW

Lung Cancer—Bad News, Good News

We have much bad news about lung cancer, but we also have some good news to give us hope for the future.

As detailed by Pett, Wernly and Akl in their elegant review of the lung cancer problem, the epidemic of this disease continues to worsen. Lung cancer remains the number one cancer killer of men and causes more deaths than the next five most common cancers of men combined: cancers of the prostate, colon and rectum, pancreas, stomach and leukemia. Lung cancer is now the most common cause of cancer death in women, having surpassed cancer of the breast for the first time in 1985.

There are a few reports, however, that promise to ease the gloom about the future. In 1979 Auerbach and associates[1] reported on a study of the precancerous changes in the bronchial epithelium of a group of men who died between 1955 and 1960 and compared them with those of a group who died between 1970 and 1977. They found serious abnormalities much less frequently in the group who died during the latter

TABLE 1.—*Lung Cancer 5-Year Survival Rates**

Years	Ethnic Groups: White, Percent	Ethnic Groups: Black, Percent
1960-1963	8	5
1970-1973	10	7
1973-1975	12	10
1976-1981	13	11

*From Cancer Statistics, 1985.[7]

period even when they analyzed, by groups, those who had smoked the same number of cigarettes per day. The difference is presumed to result from the group of men in the latter period smoking low-tar cigarettes. They suggested that the decline in the proportion of cigarette smokers with precancerous changes in the bronchial epithelium might presage a decline in the death rate due to lung cancer. These data, plus the decrease in the percent of men who smoke at all,[2] may explain the reports of decreasing death rates due to lung cancer in certain subsets of the population of the United States. Doll and Peto[3] reported that there had been a decrease in the lung cancer mortality per million American men aged 35 to 49 during the 1970s. More recently, Newell and associates studied the lung cancer death rates for men in Texas and reported that from 1970 to 1983 there were decreases in mortality for white men aged 35 to 54 and for black men aged 35 to 44.[4] A population-based study of the incidence of lung cancer in Olmsted County, Minnesota,[5] showed that the rate for men for 1965 to 1974 was 41.2 per 100,000 per year and for 1975 to 1979 it was 41.3. It seems reasonable to conclude that the epidemic of lung cancer in men is peaking out and that we may see a decline in the total male lung cancer death rate before the end of the 20th century. Unfortunately, the rates for various groups of women are continuing to increase. The good news is that the percent of women smoking is decreasing,[2] and this decrease should eventually result in a decrease in the death rate due to lung cancer.

Lung cancer is not only a huge problem but also a complex problem, with many histologic cell types of malignant neoplasms and anatomic stages of the disease. The traditional and common cell types, squamous cell carcinoma, adenocarcinoma, large-cell carcinoma and small-cell carcinoma, make up more than 90% of the cases and the deaths. These account for the epidemic, as there is no evidence of an increase in the others except for malignant mesothelioma, cases of which have increased due to the exposure of millions of people to asbestos fibers. As Pett and co-workers point out, the traditional classification into the four cell types is a simplistic solution to a complex problem. Many lung cancers contain areas typical of two or three or even all four of the cell types. Special studies such as histochemical analyses and electron microscopy do not solve the problem and, at the present time, one is forced to name a lung cancer by the predominant cell type.

Pett and colleagues point out that there are defects in the tumor-node-metastasis (TNM) system of staging lung cancer. This system was developed in the 1960s, was published in the 1970s and has been of great value in spite of its defects. Much has been learned about lung cancer in the past 20 years, and the good news is that a revision has been developed by the American Joint Committee on Cancer in cooperation with the TNM Committee of the International Union Against Cancer (Union Internationale Contre le Cancer) and several other national cancer groups.[6]

In general, the news about the treatment of lung cancer is bad, and some doubt that treatment is worth the effort. Many generalizations are published that only one in ten or even fewer survives five years. According to the American Cancer Society, however, there has been some improvement in the overall results in the past 25 years (Table 1).[7]

Some of the improvement in survival may be due to lead-time bias, but there are many data that indicate that presently available treatment is curative for various subsets of patients with lung cancer. Pett and associates give details of a report of a population-based study of patients with lung cancer showing 7% overall survival for five years, the rates varying from 11.7% for adenocarcinoma to 0% for small-cell cancer. In contrast, a population-based study of all cases from Olmsted County[5] showed five-year survival rates of 24% for squamous cell carcinoma, 18% for adenocarcinoma, 16% for large-cell carcinoma and 0% for small-cell cases. As Pett and co-workers point out, surgical resection is followed by five-year survival in more than half of the patients with resectable stage I non-small-cell lung cancer. Even those with more extensive disease may be cured by aggressive resection of the intrathoracic disease if there are no occult distant metastases. This is particularly true of those with chest wall invasion, including the Pancoast tumors, if there are no lymph node metastases and if the surgical resection is combined with appropriate adjuvant radiation therapy and in some cases multiple drug chemotherapy.[8]

Even those cases not amenable to surgical resection may be helped and some may be cured by presently available radiation therapy and chemotherapy.[9,10]

The news about small-cell lung cancer is of special interest. The bad news is that about 20% of all lung cancer is of the small-cell type—that is, about 30,000 new cases each year. The good news is that whereas this type of lung cancer was almost always fatal in the past, modern aggressive therapy combining chemotherapy, radiation therapy and, in some cases, surgical resection results in prolonged survival of many patients and actual cure of the disease in some of them.[11]

Although many patients with lung cancer cannot be cured, all of them can be helped by the judicious use of palliative radiation therapy, analgesics, antibiotics for complicating infections, therapy for concomitant diseases and compassionate emotional support of the patients, their families and their friends.[12] For the time being, physicians caring for patients with lung cancer should consider adopting as their principle

the 15th century French folk saying which guided Dr Edward Livingston Trudeau in his care of patients with tuberculosis a century ago:

To cure sometimes,
To relieve often,
To comfort always.

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Some Gods Have Feet of Clay

DURING the last few months some of the gods of modern science and technology have seemed more and more to have feet of clay. Certainly there have been, and still are, many who are worshiping these gods and all the blessings that high technology has wrought. Nonetheless, the recent series of tragic, embarrassing and costly failures in the space program of the United States and the frightening explosion of a nuclear reactor in the Soviet Union, with its almost worldwide fallout, have been very sobering events. It has been clearly demonstrated that even the best technology is only relatively dependable, and that human factors must always enter the equation, whether in exercising or not exercising human judgment, or in the human fallout when there is an unexpected technologic failure or disaster.

Perhaps these truly sobering events will focus attention once again on the humanity that pervades this world of increasingly useful yet often risky technology. We are living at a time when worship of science and technology—whether in medicine, in the production of energy, in space or wherever—has been almost pervasive throughout our society. High tech is not supposed to fail, and when it does it is held that "something went wrong," and too often there has been a tragedy.

It may not be too soon for humanity to come to more realistic terms with modern science and high technology. The issue has already come to a head in medicine, where it is being discovered that medical science and technology are not and never will be unerringly effective. Society has yet to come to grips with this reality. The fact is that in medicine there are always probabilities of success and of failure, and there is always the possibility of human error. The same holds true for nuclear reactors and the launching and operation of space vehicles. Quite evidently, this has to be true of all modern science and technology, wherever it is.

Risk is inherent in health care and in all aspects of human life. To the extent humans are free and aware, they can assess their personal risks and act accordingly. The human hope and even expectation have been that science and technology can be made risk free. But this can never be. Science and technology, and even physicians, are all useful and even necessary, but none can be infallible. A blind and unthinking faith in human and technologic perfection (which does not exist and is simply unattainable) should be replaced by thoughtful weighing of the probabilities for success or failure and, if there is failure, the likely fallout of whatever kind.

Perhaps we should now begin to ask whether, in the long run, nuclear power and war in space will be worth their risk to humanity, especially since these particular gods have now so clearly shown their feet of clay.

MSMW

Digitalis—A Bicentennial Progress Report

IN THIS ISSUE of the journal, Bhatia has nicely summarized the current status of the clinical entity of digitalis toxicity. At least four developments over the past 15 years have reduced substantially the incidence of this important clinical problem. The first of these is an improved understanding of digoxin pharmacokinetics by clinicians—in particular, an enhanced awareness of the importance of renal excretion as a determinant of the appropriate daily maintenance digoxin dose. Second, serum digoxin concentration measurements are now widely available in clinical laboratories. While overutilized at times, such data are useful in the assessment of unexpected responses to digoxin therapy. Third, the bioavailability of digoxin in preparations for oral use is now far more uniform since the introduction of explicit standards by the Food and Drug Administration (FDA) and the United States Pharmacopeial Convention. And, fourth, improvements in the therapeutic armamentarium for management of congestive heart failure (such as loop diuretics and vasodilators) and supraventricular tachyarrhythmias (such as β-adrenergic blocking agents and the calcium channel blockers verapamil and diltiazem) now render largely obsolete the practice of "pushing" digitalis glycoside doses to maximal tolerated levels. Regarding this last point, there is no solid evidence from clinical studies to indicate that further inotropic benefit is realized by pushing serum concentrations of digoxin above the 1.5 to 2.0 ng per ml range, whereas there is no doubt that the incidence of overtly toxic rhythm disturbances increases substantially as levels higher than this are reached.

Lindenbaum and his colleagues in New York have discovered that about 30% of patients on maintenance digoxin therapy harbor in their lower gastrointestinal tract the saprophytic bacterium *Eubacterium lentum*, which has the enzymatic capacity to convert digoxin to the cardioinactive metabolite dihydrodigoxin and thus to hasten the effective clearance of digoxin. This is quantitatively of clinical importance in at least 10% of patients on a digoxin regimen, who are at risk of a potentially significant increase in their serum

and total body digoxin stores if they receive any of a wide range of antibiotics that rid the gut of *E lentum*.[1]

While all of the above advances in our sophistication regarding the clinical pharmacology of digoxin render the drug safer to use, the fact that 4 million patients in the United States are receiving maintenance digoxin, together with the notoriously narrow margin between therapeutic and toxic doses, ensures that clinically important digitalis toxicity will remain a common problem for the foreseeable future—especially in patients with advanced heart disease in whom it is particularly difficult to distinguish among rhythm disturbances due to digitalis excess, to underlying heart disease or to a combination of both.

Among the noteworthy achievements of the past decade is a much improved understanding of the actions of digitalis glycosides at the cellular level. It has been known for about 25 years that cardiac glycosides inhibit with high affinity and specificity the sodium pump of intact cells; the binding site or "receptor" is now known to reside at an extracellularly facing locus on the α-subunit of sodium-potassium-adenosine triphosphatase, a protein that has now been cloned and sequenced.[2] Occupancy of the receptor blocks the normal outward transport of three Na^+ ions in exchange for the inward transport of two K^+ ions, a process that uses the free energy from cleavage of the terminal high-energy phosphate of adenosine triphosphate to drive these ions uphill against their concentration gradients. In therapeutic (subtoxic) doses, enough pump sites are blocked to produce a modest increase in intracellular Na^+ activity. Through the phenomenon of Na^+-Ca^{++} exchange, this augments intracellular Ca^{++} content and thus enhances contractile force of both normal and failing heart muscle. These same phenomena—sodium-potassium pump blockade and increased intracellular calcium stores—occur to a quantitatively greater degree in the presence of digitalis excess, and underlie the toxic rhythm disturbances that Bhatia has summarized. At still higher and more toxic doses, hyperkalemia can occur (usually in suicidal or accidental overdoses) with ominous prognostic significance.

Bhatia's discussion of the use of purified digoxin-specific Fab fragments in the management of advanced, life-threatening digitalis toxicity is timely in view of the recent approval by the FDA of the release of this new therapeutic modality (generically termed digoxin immune Fab [ovine], or Digibind by Burroughs Wellcome Co.). It is now ten years since we treated the first patient with digoxin-specific Fab fragments derived from sheep polyclonal antibodies,[3] and the subsequent experience in more than 150 patients so treated continues to be gratifying.[4] One cannot resist noting on the frontispiece of William Withering's "Account of the Foxglove and Some of Its Medical Uses," published in 1785, his use of the following quotation from the Ars Poetica of Horace: "*. . . nonumque prematur in annum,*" freely translated "let it be held back until the ninth year." This admonition of Horace to poets not to hasten to press with their work now appears equally apropos of Withering's cautious reporting of his new medicine for treatment of dropsy and of the protracted nature of the development and regulatory agency approval of current therapeutic advances.

For the present, we foresee that the use of digoxin-specific Fab fragments from the polyclonal sheep source will be reserved for potentially life-threatening situations that are (or seem likely to be) resistant to conventional therapeutic modalities. It is appealing to consider the use of similar immunologic approaches to diagnostic as well as therapeutic problems—that is, to use a suitable Fab (or smaller) binding fragment in a sort of "reverse acetyl strophanthidin tolerance test" in which the assured diagnosis that a given rhythm disturbance is due to digitalis intoxication would accompany the abolishment of the arrhythmia. This would be best accomplished using a molecule with appropriate affinity and specificity for cardiac glycosides, but with human immune specificity and hence no risk of development or expression of hypersensitivity. Detailed sequence information on monoclonal antidigoxin antibodies is already available[5] and could in principle be coupled with recombinant DNA technology to yield chimeric antibodies or antibody fragments with selected variable regions joined to different isotypic constant regions.[6]

For the future, there is ample room for improvement in the clinical use of digitalis glycosides. Issues as fundamental as the proper indications for the use of digoxin remain controversial, although a strong consensus now exists that the drug should be used in cases of heart failure for the subset of patients with dilated ventricles that contract poorly, and not in patients with normal-sized left ventricles that contract well but are "stiff" or noncompliant, thus producing dyspnea from elevated filling pressures. Patients with coronary heart disease as well as left ventricular hypertrophy from a variety of causes commonly fit into this latter category and, in general, should not be treated with cardiac glycosides unless supraventricular rhythm disturbances provide an appropriate rationale.

Further refinement of therapeutic indications should be based on randomized trials with stratification for such important variables as age and type and severity of heart disease. In particular, the *incremental* risks and benefits of cardiac glycoside therapy over and above other available modalities including diuretics and vasodilators deserve attention.

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Case Reports

Intravenous Marijuana Syndrome

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THE INTRAVENOUS (IV) INJECTION of boiled marijuana broth causes a distinct clinical syndrome. To date, 24 cases of this syndrome have been reported in the English language literature.[1-9] We report the 25th case and review the literature.

Report of a Case

In mid-January 1983, a 26-year-old man was evaluated at Providence Medical Center (Portland) for fever, myalgias, nausea and vomiting. He had boiled marijuana, strained the broth through cotton and injected it into his antecubital vein. One hour later, he had cough, nausea, vomiting, diarrhea, pain in his back and legs and fever. These symptoms persisted, and after 3½ hours he came to the emergency room. He had injected marijuana once previously and experienced pleasant psychological effects only. He had occasionally used LSD, cocaine and hydromorphone hydrochloride (Dilaudid) by nonintravenous routes, but denied other recent drug use. His past history was otherwise unremarkable. On physical examination he had a blood pressure of 60/40 mm of mercury, a heart rate of 110, a temperature by mouth of 40.8°C (105.4°F) and tender, weak arm musculature.

Initial laboratory studies elicited the following values: hematocrit 43.8%; leukocyte count 6,000 per μl, of which 69% were polymorphonuclear leukocytes and 23% bands; platelet count 209,000 per μl; creatinine 1.8 mg per dl; blood urea nitrogen (BUN) 17 mg per dl; potassium 3.6 mEq per liter; phosphate 1.5 mg per dl; asparate aminotransferase 28 IU per liter; lactic dehydrogenase 259 IU per liter, and creatine kinase (CK) 236 IU per liter. Urinalysis showed 30 mg per dl of protein. The chest x-ray film and electrocardiogram were normal. The arterial pH was 7.41.

The patient was admitted, given normal saline intravenously and treated empirically with a regimen of nafcillin sodium and tobramycin. Over the first 24 hours he received six liters of fluid and had a urine output of four liters. Despite a blood pressure of 70/50 mm of mercury, the central venous pressure measured 12 cm of water. Administration of dopamine hydrochloride was begun. On the evening of admission the leukocyte count fell to 1,500 per μl and the phosphate level to 0.5 mg per dl. By day 2 he had become afebrile and his blood pressure had risen to 100/70 mm of mercury on a regimen of 11 μg per kg per minute of dopamine. Repeat CK level measured 2,340 IU per liter, 2.7% of which was of the MB fraction; a serum myoglobin level was 435 ng per ml (normal 6 to 83), urine myoglobin 1,950 ng per ml, serum creatinine 2.4 mg per dl and serum phosphate 2.1 mg per dl. On day 3 his blood pressure was 100/60 mm of mercury off dopamine therapy, leukocyte count 26,000 per μl and platelet count 93,000 per μl. Cultures were negative after 48 hours and antibiotic therapy was discontinued. On day 5 he was discharged. One week later the serum creatinine level had fallen to 1.4 mg per dl, the CK level to 70 IU per liter and all symptoms had resolved.

Discussion

In 1968 Henderson and Pugsley first described the syndrome of emesis, myalgia and hypotension following the IV injection of broth derived from boiled marijuana.[1] In the present report we describe the 25th case of this syndrome. There have been 16 additional reports of such cases in sufficient detail to allow a review of clinical and laboratory features (Table 1). We have assumed that a feature was absent if not noted by the author; thus, the percentages in the table represent minimum figures. Symptoms began within a half hour in 14 and within an hour in all 17 cases. Initial symptoms included myalgia, nausea and vomiting, diarrhea, abdominal pain and weakness. Presenting signs involved tachycardia, hypotension, fever, tachypnea, muscle tenderness and hepatomegaly. Muscle weakness was not clearly shown. Of interest is that 15 patients had a normal mental state. All patients required IV administration of fluid and five required vasopressors for maintaining blood pressure. All 25 patients survived; the mean reported hospital stay was 9.1 days.

Several laboratory findings are noteworthy (Table 1). Leukocyte counts ranged from 1,100 to 41,000 per μl. Of 17 patients, 14 had pronounced leukocytosis of greater than 20,000 per μl,[1,2,4,6-9] while three manifested early leukopenia.[2,3] Platelet counts were less than 100,000 per μl in eight patients.[1,2,6,7,9] Azotemia was present in 14, with a mean BUN level of 75 mg per dl and a mean creatinine value of 5.8 mg per dl for 8 patients for whom a value was reported.[1-3,6-9] In six cases, an elevated bilirubin level (mean 4.1 mg per dl for ten patients)[1-3,6,7,9] or a CK level[2,7,9] or a pulmonary abnormality[1-3,7,9] was noted.

The pathophysiology of this syndrome remains unclear. While hypotension may be partially due to hypovolemia resulting from diarrhea and emesis, evidence of vasodilation has been noted clinically and may be the major mechanism.[9] While sepsis has been considered, bacteremia has not been found, though circulating endotoxin has not been excluded as a possible mechanism. In a study in which normal subjects were given cannabinoids intravenously, the components of marijuana responsible for more typical somatic and psychological changes, neither hypotension nor other adverse effects described above were induced.[10] Similarly, our patient had no apparent toxicity from a previous marijuana injection. Because the specific composition of the material injected by the

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ABBREVIATIONS USED IN TEXT

BUN = blood urea nitrogen
CK = creatine kinase
DIC = disseminated intravascular coagulation
IV = intravenous

25 patients is unknown, it is possible that the dose exceeded that given the normal experimental subjects or that a contaminant may have been responsible for the somatic toxicity. In at least seven cases, cotton was used to strain the broth before injecting.[2,3,7,8] "Cotton fever" has been reported following the IV use of heroin reclaimed from previously used cotton filters[11] and consists of emesis, myalgia and fever; thus, it partially resembles the IV marijuana syndrome.

The combination of diffuse myalgia and an elevated unfractionated serum CK level suggests the presence of rhabdomyolysis in five previously reported cases.[2,7,9] We have documented elevations of serum and urine myoglobin levels in addition, confirming specifically for the first time the presence of rhabdomyolysis and myoglobinuria as part of this syndrome. The precise mechanism of the muscle necrosis in these patients is unclear. Hypotension, fever and substantial hypophosphatemia were present in the case reported herein and may have been pathogenic.[12] Alternatively, a direct effect of the injected material cannot be excluded. In this regard, it is of interest that severe rhabdomyolysis has occurred, in the absence of pressure necrosis, following the intravenous use of adulterated heroin.[13]

The patients' renal insufficiency can be attributed to several factors, including a prerenal component due to volume depletion, acute tubular necrosis due to hypotension and myoglobinuria. In addition, creatine released from injured skeletal muscle cells and spontaneously converted to creatinine may contribute to the elevated levels of the latter in serum of those patients with rhabdomyolysis.[14] In two cases, a low fractional excretion of sodium was found, consistent with prerenal azotemia.[9] Renal function uniformly improved after administering fluid alone, or fluid and mannitol. While the reports are unclear in regard to the duration of renal impairment or the degree of recovery, no patient has required dialysis.

TABLE 1.—*Features of the Intravenous Marijuana Syndrome**

Features	Patients Number	Percent	References
Symptoms			
Myalgia	16	94	1-3,6-9
Nausea, vomiting	16	94	1,2,6-9
Diarrhea	15	88	1,2,6-9
Abdominal pain	11	64	1,2,6-9
Weakness	8	47	1,2,6,7,9
Signs			
Tachycardia	14	82	1-3,6-9
Hypotension (systolic <90 mm of mercury)	14	82	1-3,6-9
Fever (>38.3°C [101°F])	7	41	2,3,6-8
Tachypnea (RR>21)	7	41	2,3,7-9
Muscle tenderness	6	35	2,7,9
Hepatomegaly	4	24	1-3
Altered sensorium	2	12	3,6
Laboratory			
WBC >20,000/μl	14	82	1,2,4,6-9
WBC <4,000/μl	3	18	2,3
Platelets <100,000/μl	8	47	1,2,6,7,9
Azotemia†	14	78	1-3,6-9
↑ CK	6	35	2,7,9
↑ Bilirubin	6	35	1-3,6,7,9
Pulmonary abnormality‡	6	35	1-3,7,9

CK = creatine kinase, RR = respiratory rate, WBC = leukocyte count

*Compiled from data on the patient in this report and 16 cases reported in sufficient detail in the literature. It should be noted that the percentages represent minimum figures because features were assumed to be absent if not mentioned in the reports.
†Creatinine level >1.2 mg/dl or blood urea nitrogen level >21 mg/dl.
‡Abnormalities of chest film, ventilation-perfusion scan or arterial blood gas values.

The thrombocytopenia of this syndrome may be a result of disseminated intravascular coagulation (DIC), which occurs commonly in cases of major rhabdomyolysis.[14] Of five patients with thrombocytopenia who were tested for a partial thromboplastin time, three had prolonged times.[7,9] Further testing of these three patients elicited values for fibrin-degradation products and a prothrombin time consistent with DIC in two cases.[9] Three additional patients have been evaluated by serial assays of factors I, II, V, VII, IX and X. No factor consumption was found, suggesting strongly that DIC was not present.[4] Similarly, when marijuana broth was injected into rabbits, thrombocytopenia ensued in the absence of clotting factor consumption.[4] Thus, the precise role of DIC as a cause of thrombocytopenia in these patients remains unclear; a direct platelet-lowering effect of the injected material remains a possibility.

Pulmonary abnormalities have included mild hemoptysis (n = 1),[1] an elevated alveolar-arterial gradient (n = 1),[2] congestion on chest films (n = 4)[2,3,9] and pleural effusion (n = 1).[9] In the case of one patient with hypoxemia and a diffusely hazy appearance on chest x-ray film, ventilation-perfusion lung scanning showed a nonsegmental variation in blood flow, interpreted as consistent with a diffuse pulmonary vascular process.[9] Capillary leak, pulmonary microvascular embolization of injected particulates and DIC have been suggested as possible mechanisms for the pulmonary abnormalities.[9]

Finally, hyperbilirubinemia and hepatomegaly, found in a few cases, were investigated with a liver biopsy in two. The biopsy specimens showed acute and chronic inflammation, necrosis about the limiting plate, foci of hepatocellular dropout and no foreign bodies. In both cases, liver enzyme values spontaneously improved.[7]

To summarize, in 25 people a reversible multisystem illness developed, characterized by gastrointestinal and myopathic symptoms, tachycardia, hypotension and fever, following the intravenous injection of boiled marijuana preparations. Rhabdomyolysis, renal insufficiency and hematologic, pulmonary and hepatic abnormalities have occurred during the week following IV injection. All patients recovered completely with supportive therapy alone. While selected features of the syndrome may be due to concomitant injection of contaminants or extremely high doses of cannabinoids themselves, the pathogenesis of the IV marijuana syndrome remains unclear.

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Reactivation of Coccidioides Infection

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THE LIST of causes of pulmonary infection in an immunocompromised host is long and continues to grow. Reactivation of prior subclinical coccidioidomycosis is rare. We report two cases of coccidioidomycosis in renal transplant recipients, occurring in a nonendemic area during the hospital stay immediately following transplantation. One patient had coexisting *Pneumocystis carinii* pneumonia.

Reports of Cases

Case 1

The patient, a 40-year-old man, had chronic renal failure due to Alport's syndrome. He was maintained on long-term hemodialysis therapy until he came to San Francisco from Salt Lake City for renal transplantation. He had lived for a few years in Pasadena, California, 20 years before presentation. There was no history of coccidioidomycosis or childhood pneumonia. Results of a pulmonary evaluation including a chest x-ray film were normal on admission to the University of California, San Francisco. He received a living-related donor kidney transplant in late January 1983. Immunosuppression with prednisone (1.5 mg per kg per day) and azathioprine (50 to 150 mg per day) was begun. On the sixth day after transplantation, the prednisone dosage was increased to 3 mg per kg per day, and on the ninth day a six-dose course of antithymocyte globulin was begun for acute transplant rejection. The prednisone dosage was then tapered to 1 mg per kg per day over three weeks.

In the third week of hospital stay, dyspnea on exertion developed. The next day he had cough with minimal hemoptysis and dyspnea at rest. The patient was afebrile with a respiratory rate of 18 breaths per minute. Rales and egophony were noted on chest auscultation. The leukocyte count was 5,400 per μl. Arterial blood gas determinations showed an arterial partial pressure of oxygen of 67 torr, arterial partial pressure of carbon dioxide of 30 torr and pH 7.42. There were diffuse nodular infiltrates on the chest roentgenogram without mediastinal or hilar lymphadenopathy (Figure 1). Sputum evaluation was not revealing. On bronchoscopic examination there were spherules consistent with *Coccidioides immitis* on frozen section examination of the transbronchial biopsy specimens. Culture of these specimens subsequently grew the fungus. The prednisone dosage was reduced to 30 mg per day, azathioprine therapy was discontinued and a course of amphotericin B was begun. A brief period of mechanical ventilation was required for hypoxemia. Sputum cultures became negative for *C immitis* after two months of therapy (2.6 grams of amphotericin B). Chest films showed slow improvement, but at discharge there remained reticulonodular infiltrates. Counterimmunoelectrophoresis for coccidioidomycosis was negative at the onset of infection and at five weeks, but was positive at nine weeks. The complement fixation (CF) titer was less than 1:4 throughout the nine-week period of observation. The patient returned to Utah for follow-up care.

Case 2

The patient, a 35-year-old man with insulin-dependent diabetes mellitus and renal failure, had been receiving hemodialysis for two years before admission. In addition, he had hypertension, diabetic retinopathy and peripheral neuropathy. There was no history of coccidioidomycosis or childhood pneumonia. He lived in Bakersfield, California (endemic for *C immitis*), until age 25 and had been living in San Jose, California (not endemic), since that time.

The patient underwent cadaveric renal transplantation in August 1983, and was placed on a regimen of prednisone, 2.5 mg per kg per day, and azathioprine, 150 mg per day, until the third week after transplantation, when the prednisone dosage was decreased to 1 mg per kg per day and azathioprine

Figure 1.—Chest radiograph of the patient in case 1 showing diffuse nodular infiltrates due to *Coccidioides immitis* infection.

(Seltzer J, Broaddus VC, Jacobs R, et al: Reactivation of coccidioides infection. West J Med 1986 Jul; 145:96-98)

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to 75 mg per day. During the fourth week daily antithymocyte globulin therapy was begun for a total of 14 days following transplantation. Tapering of the azathioprine and prednisone dosages continued, however, and he was finally maintained on a regimen of prednisone, 45 mg per day, and azathioprine, 25 mg per day.

During the sixth week following transplantation, while still in hospital, his temperature rose to 38°C (100.4°F). Sputum evaluation was negative. A chest x-ray film 12 days later continued to show no pulmonary infiltrates. After another nine days (nine weeks after transplantation) his temperature increased to 40°C (104°F) associated with dyspnea; a chest film showed diffuse, poorly defined nodular densities with right hilar and right paratracheal fullness (Figure 2). Azathioprine therapy was discontinued, the prednisone dosage was decreased to 30 mg per day and a regimen of amphotericin B and trimethoprim-sulfamethoxazole was begun empirically. Bronchoscopy with transbronchial biopsy was done. Culture of the transbronchial biopsy specimen grew *C immitis* and silver methenamine stains of this specimen and lavaged lung secretions showed *Pneumocystis carinii*. The patient was treated with a regimen of trimethoprim-sulfamethoxazole for three weeks and amphotericin B for eight weeks. The *Coccidioides* CF titer was positive at 1:64. After 1.25 grams of amphotericin B, the CF titer had risen to 1:512 and, at the time of discharge, after 1.6 grams of amphotericin B, the CF titer was 1:256. The chest x-ray film showed slight improvement after one week of therapy and remained stable until discharge. He was discharged on a regimen of ketoconazole.

Two months after discharge, the chest film continued to show multiple small nodules, little changed from findings at discharge, and some decrease in the hilar and paratracheal adenopathy. The complement fixation titer at three months after discharge was 1:32.

Figure 2.—Chest radiograph of the patient in case 2 showing poorly defined nodular densities with right hilar and right paratracheal fullness. Bronchoscopy led to a diagnosis of coccidioidomycosis and *Pneumocystis carinii* pneumonia.

Discussion

These two cases of coccidioidomycosis occurring in immunocompromised patients in hospital stress the importance of considering reactivation of latent coccidioidomycosis in any immunocompromised patient who had resided in or traveled to an endemic area.

In several reviews and case reports of coccidioidal infections in compromised hosts,[1-6] the need to consider reactivation of coccidioidal infection in this situation has been emphasized. There are few cases, however, in which there was no history or radiographic evidence of prior coccidioidomycosis infection. The most unequivocal cases of reactivated coccidioidomycosis are those that occur in a hospital or area located well outside of an endemic region. Our cases belong in this category and there are six other such cases in the literature.[3,5,7-10] Like our patients, three of these patients[3,5,10] had no history of coccidioidomycosis.

The occurrence of coccidioidomycosis in immunosuppressed patients is well documented, but most of the reported cases occurred in patients living in endemic areas. Without a documented history of prior coccidioidal disease, it is often impossible to determine if disease is due to primary infection or reactivation of quiescent disease. Even if a history of prior disease is well documented, active disease could conceivably be due to reexposure—that is, exogenous reinfection. This mode of infection has not been well documented but may occur in laboratory workers with a history of positive skin test who receive heavy exposure in the laboratory.[2] There is also evidence that immunocompromised patients are more susceptible to primary infection than nonimmunocompromised patients. Cohen and co-workers[11] examined the incidence of coccidioidomycosis infection in renal transplant recipients over a nine-year period in Arizona and found that this group had a fourfold increased risk of symptomatic coccidioidomycosis developing. The risk of disseminated coccidioidomycosis is likewise greater in immunocompromised patients (50% to 80%) than in nonimmunocompromised patients (15%).[12]

In both of our cases, infection developed following a course of antithymocyte globulin. Administration of this drug has not been reported to increase the susceptibility of immunocompromised patients to opportunistic infections, but among the cases reviewed, only one[8] had received the drug.

It is of interest to note that one of our patients had coexisting *Pneumocystis carinii* pneumonia. This combined infection has recently been reported in a patient with the acquired immunodeficiency syndrome.[13]

In summary, we have presented two cases of coccidioidomycosis occurring while the patients were being treated in hospital in a nonendemic area following renal transplantation. The diagnosis of reactivated coccidioidomycosis should be considered in the differential diagnosis of pulmonary infiltrates of any immunocompromised patient with a history of travel or residence in an endemic area.

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Pseudoinfarction in Patients With Massive Pulmonary Embolism

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PULMONARY EMBOLISM is a common fatal disease, but the antemortem diagnosis is frequently missed. We report two cases in which the diagnosis of massive pulmonary embolism was obscured by clinical and electrocardiographic signs suggestive of acute myocardial infarction.

Reports of Cases

Case 1

The patient, an 80-year-old man, was admitted for cardiovascular collapse. He had had an unremarkable medical history until the day before admission, when he had nonspecific complaints. The morning of admission dyspnea developed and he became unconscious and cyanotic. Paramedics found a palpable systolic blood pressure of 86 mm of mercury, a pulse of 98 beats per minute, respirations of 6 per minute and diffuse rales. Third-degree atrioventricular (AV) block occurred, and resuscitative measures were initiated.

On arrival to the emergency room, arterial blood gas determinations with the patient breathing room air showed a pH of 7.16, a partial carbon dioxide pressure (P_{CO_2}) of 57 torr and a partial oxygen pressure (P_{O_2}) of 15 torr. An endotracheal tube was inserted, 100% oxygen was started and a temporary pacemaker was implanted. Repeat blood gas values were pH 7.08, P_{CO_2} 59 torr and P_{O_2} 163 torr. Two episodes of ventricular fibrillation occurred requiring cardioversion and administration of bretylium tosylate. The 12-lead electrocardiogram is shown in Figure 1-A.

(Denton TA, Litvack F, Siegel RJ: Pseudoinfarction in patients with massive pulmonary embolism. West J Med 1986 Jul; 145:98-101)

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ABBREVIATIONS USED IN TEXT

AV = atrioventricular
P_{CO_2} = partial carbon dioxide pressure
P_{O_2} = partial oxygen pressure
TTC = triphenyl tetrazolium chloride

The blood pressure was then 138/50 mm of mercury and the rhythm was sinus at a rate of 124. On physical examination he had jugulovenous distention, diffuse rales and distant heart sounds. A Swan-Ganz flow-directed pulmonary arterial catheter was inserted and initial pressures were as follows: mean right atrial 12 mm of mercury, pulmonary artery 49/30 mm of mercury (mean 36) and mean pulmonary capillary wedge pressure 35 mm of mercury. Repeat blood gas determinations showed pH 7.36, P_{CO_2} 42 torr and P_{O_2} 365 torr. Ventricular tachycardia and ventricular fibrillation recurred requiring cardioversion. A second 12-lead electrocardiogram was done and is shown in Figure 1-B. Electromechanical dissociation and ventricular fibrillation unresponsive to therapy ensued, and the patient died five hours after initial collapse.

At autopsy, gross examination of the lungs showed multiple large pulmonary emboli, the source of which was a thrombophlebitis of the left leg venous system. On postmortem coronary angiography, there were normal coronary arteries without occlusion or narrowing. Gross examination of the myocardium showed no abnormalities and histochemical staining with triphenyl tetrazolium chloride (TTC) showed no infarction. There was no light-microscopic evidence of significant coronary artery disease or myocardial infarction.

Case 2

The patient, an 85-year-old woman, was admitted because of vomiting for two days. She had chronic hypertension and atrial fibrillation, for which she was being treated with a regimen of Dyazide,* digoxin and verapamil. She had nausea and vomiting for two days but said she did not have chest pain or shortness of breath. Initial blood gas determinations with the patient receiving 4 liters of oxygen per minute showed a pH of 7.51, a P_{CO_2} of 35 torr and P_{O_2} 104 torr. The electrocardiogram showed an anterior wall myocardial infarction pattern (Figure 2) with associated involvement of the right ventricle (ST elevation in leads V_{2R}, V_{3R} and V_{4R} not shown).

Shortly after admission, third-degree AV block developed, and she had subsequent ventricular fibrillation, which responded to cardioversion. The blood pressure was 100/40 mm of mercury, and the pulse was 65 beats per minute. The mean right atrial pressure was 4 mm of mercury, pulmonary artery pressure was 30/15 mm of mercury, the mean pulmonary capillary wedge pressure was 10 mm of mercury and cardiac output was 1.3 liters per minute. Repeat blood gas measurements while the patient was breathing 100% oxygen showed a pH of 7.35, P_{CO_2} 25 torr and P_{O_2} 42 torr. The patient continued to have hypoxia and hypotension with no change in her intracardiac pressures, and she died in electromechanical dissociation 24 hours after admission.

At autopsy there was a large embolus in the right pulmo-

*A Smith Kline & French combination product containing 50 mg of triamterene, a potassium-sparing agent and 50 mg of hydrochlorothiazide.

nary artery and no source could be found. Serial sectioning of the epicardial coronary arteries showed no significant occlusions or narrowing. Gross, histochemical (TTC) and light-microscopic study of the myocardium showed no myocardial infarction.

Discussion

Difficulty in the clinical diagnosis of pulmonary embolism is well appreciated as 50% to 70% of emboli are diagnosed only at postmortem.[1,2] In patients with pulmonary embolization, the history is often not helpful.[3] The most prevalent symptom is dyspnea, which is present in 85% of cases.[4,5] With massive embolization, 70% to 80% of patients will present with cardiovascular collapse, 22% with chest pain, 20% with transient cyanosis and 65% with rales.[6,7] The clinical presentations and electrocardiographic findings in our two patients were compatible with acute myocardial infarction or pulmonary embolism.

Both patients had hemodynamic measurements consistent with severe left ventricular dysfunction. The patient in case 1 had systemic hypotension, elevated wedge pressure and elevated pulmonary artery pressures. Because low wedge pressures are usual in cases of embolism,[8] the diagnosis was not considered. The patient in case 2 had systemic hypotension and "normal" intracardiac pressures but a very low cardiac output. The pulmonary vascular resistance was retrospectively calculated at 615 dynes per cm, which is eight times normal. Acidosis,[9,10] hypoxemia,[11] impaired left ventricular diastolic compliance,[12] a reverse Bernheim effect[13,14] or right ventricular failure[15] may have been factors contributing to left ventricular dysfunction in these patients. In a dog model, an elevated wedge pressure can be seen with pulmonary embolism if the balloon enters the vasculature that is occluded.[16] This could produce "falsely" elevated pulmonary wedge pressures but not other signs of poor left ventricular performance. The hemodynamic tracings were of adequate quality to exclude balloon entrapment as a cause of atypical hemodynamic parameters (Figure 3). Another hemodynamic finding that may occur in patients with massive pulmonary embolism but was not seen in our patients is the presence of a right atrial pressure that may be equal to or exceed the pulmonary capillary wedge pressure, thus complicating further the interpretation of the hemodynamics.

Electrocardiographic findings in pulmonary embolism are neither sensitive nor specific.[17] The electrocardiogram is not diagnostically useful in 80% of cases of pulmonary emboli,[18,19] though it is abnormal in 80% to 94% of patients with massive embolizations.[18,20] A pulmonary embolism may show "pseudoinfarction"[8,21-24] and simulate anterior wall[3] or inferior wall[20,25] myocardial infarction. Table 1 shows many of the electrocardiographic changes associated with pulmonary embolism.[2,7,17,18,20-29] The most common findings are $S_1Q_3T_3$, right bundle branch block, P pulmonale or right axis deviation,[20] which may be seen in 32% of cases of massive pulmonary embolism. Classification by major and minor criteria[30] and by electrocardiographic scoring systems[31] has been used to aid in the diagnosis of pulmonary embolism but has not been useful in increasing the sensitivity or specificity of the findings.

Many hypotheses exist as to the cause of the electrocardiographic changes. These include hypoxia, impaired coronary perfusion, right ventricular dilatation associated with pulmonary hypertension, anatomic rotation, vagal effects, sympathetic nervous system effects, circulating humoral effects and the diaphragmatic position.[30] With the exception of atrial arrhythmias and transient low voltage, all of the electrocardiographic changes may be accounted for merely by axis shift and strain.

Hypoxemia has been hypothesized as one mechanism,[32,33] though there is no correlation between arterial Po_2 and electrocardiographic changes except in cases of a rightward axis[20] and chronic obstructive pulmonary disease.[34] Hypotensive effects on coronary flow[35] or the pulmonocoronary reflex spasm[33] are mechanisms that may account for some electro-

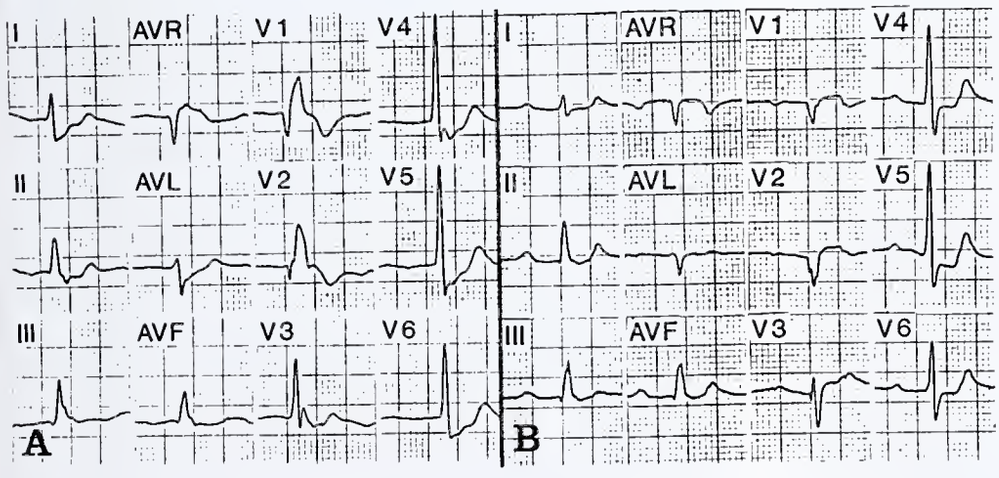

Figure 1.—A, The initial electrocardiogram done on patient 1 shows atrial fibrillation at a rate of 70 per minute, a QRS axis of 90 degrees, right bundle branch block, ST-segment depression in leads I, II and V_4 through V_6 and anterior Q waves. This was interpreted as showing acute anterior myocardial infarction but incorrectly so. The differential diagnosis should have included pulmonary embolism. **B,** A second electrocardiogram done on patient 1 shows normal sinus rhythm with first-degree atrioventricular block at a rate of 100 per minute, a QRS axis of 83 degrees, nonspecific intraventricular conduction delay (complete loss of the right bundle branch block), QS in V_1 and V_2, clockwise rotation and ST-segment depression laterally. This was interpreted as evolution of the anterior myocardial infarction seen in the previous electrocardiogram. Again, the original interpretation was incorrect and the differential diagnosis broadened to include pulmonary embolism.

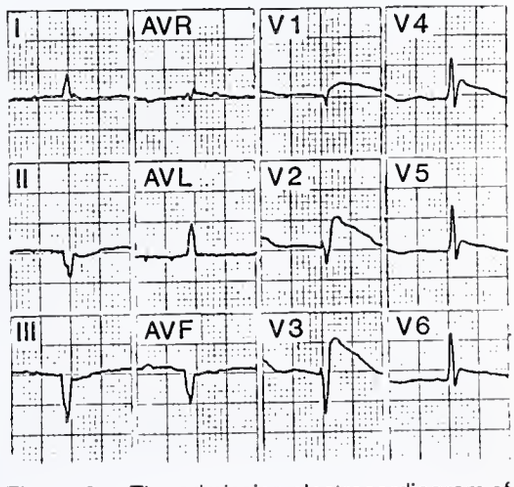

Figure 2.—The admission electrocardiogram of patient 2 shows a junctional rhythm, left axis deviation, inferior wall infarction pattern, anterior ST-segment elevation pattern and nonspecific T-wave changes. This was interpreted, inappropriately so, as an anterior wall infarction with extension to the right ventricle.

cardiographic changes. Stein and co-workers,[32,33] however, have shown clear increases in circumflex and right coronary artery flow after experimentally induced embolism in animals. Furthermore, electrocardiographic changes occur in the absence of hypotension,[20] which would argue against shock as the primary process.

Ischemia has been proposed as a mechanism because of the ST-T-wave changes found. One pathologic study has shown subendocardial necrosis in patients with normal coronaries and pulmonary embolism, but myocardial damage is not a common finding in this situation.[33]

The so-called ischemic electrocardiographic changes may be due to the strain patterns associated with right ventricular dilatation, high right ventricular pressures and dilatation of the right atrium. Strain is defined as an S wave in lead I and Q waves in leads III and aV_F, rightward frontal plane axis, T-wave inversion in leads III and aV_F, clockwise rotation in the horizontal plane, T-wave inversion in the right precordial leads, enlarged P waves, right ventricular conduction delay and atrioventricular block (first degree).[19] Such strain patterns have been found in human clinical studies after cross clamping the pulmonary artery during thoracotomy.[36] Other clinical studies have shown that increased pulmonary arterial pressure and right ventricular end-diastolic pressure are associated with the classic electrocardiographic changes of massive pulmonary embolus.[20] Right ventricular strain may be the first electrocardiographic finding in massive pulmonary embolism, which is seen in 15%[18] and related to the severity of the obstruction. But it is not usually seen until a mean pulmonary artery pressure of 30 to 40 mm of mercury is reached.[19] Strain may be further subdivided into systolic overload (usually associated with tall R waves and inverted T waves) and diastolic overload (right bundle branch block).[17]

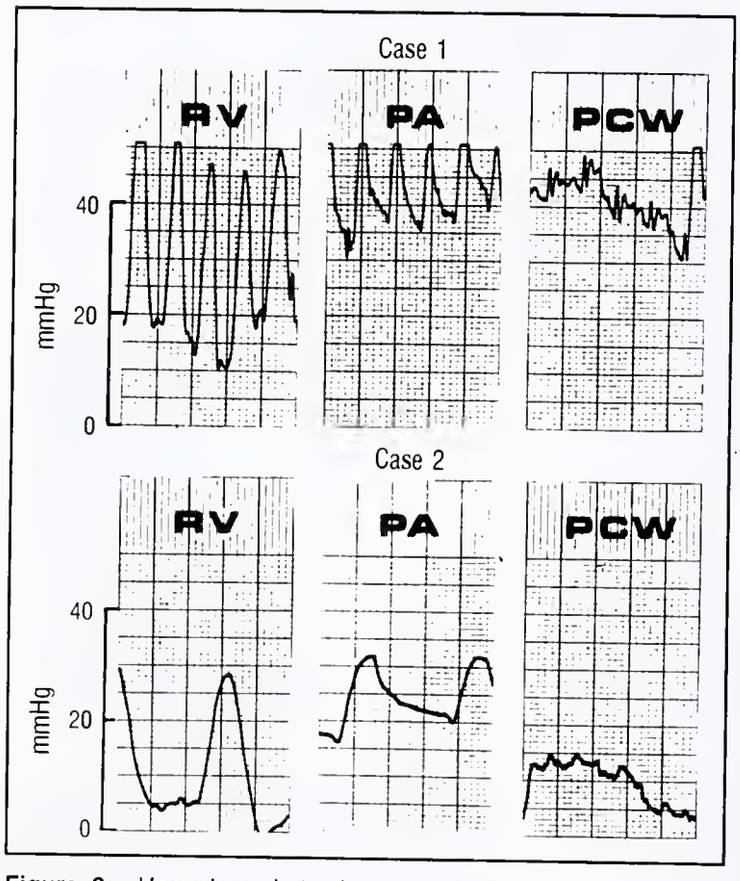

Figure 3.—Hemodynamic tracings from the patients verifying adequate balloon placement and lack of entrapment in the pulmonary artery blocked by the embolus; note the presence of a and v waves. mmHg = millimeters of mercury, PA = pulmonary artery, PCW = pulmonary capillary wedge, RV = right ventricle. The lefthand scale is in millimeters of mercury. The tracing for case 1 was run at 10 mm per second and for case 2 at 25 mm per second.

Axis shift arises from a change in the position of the right ventricle. Acute dilatation of the right ventricle displaces the rest of the heart, thus altering the electrical axis to the right. The shift is transient and generally reverts to normal within 30 days.[25] Similarly, the $S_1Q_3T_3$ and $S_1S_2S_3$ patterns, rightward axis and clockwise rotation may be accounted for by anatomic shift.

Sinus tachycardia seen in pulmonary embolus is nonspecific and may be due to hypoxemia, pain, right atrial dilatation or right heart failure, though this is not well studied. The cause of the low voltage seen in some cases is unclear. Explanations include hyperexpansion of the lungs in patients with chronic obstructive pulmonary disease or overall amplitude decrease in depolarization activity, which is associated with circulatory stress.[37] Atrial arrhythmias have been attributed to atrial dilatation, vagal influence, ischemia, catecholamines and sympathetic discharge.[30]

Both of the patients presented here had transient third-degree AV block. First-degree AV block has been described in the past but it is an uncommon finding. We can only speculate that this high-grade dysrhythmia was associated with the severe cardiovascular compromise and not a direct consequence of the embolism itself. The incidence of AV block in patients with massive pulmonary embolism is low and has not been noted in experiments in animals. In addition, there are no data on pacing requirements and the prognosis in patients who present with this problem. We might speculate that the prognosis is grave as both of the patients in the cases presented here had AV block and died.

TABLE 1.—*Electrocardiographic Changes Seen in Patients With Pulmonary Embolism**

Strain Pattern	
ST elevation (16%)	Right ventricular hypertrophy
aV_R, V_1 to V_3	Right atrial enlargement
ST depression (25%)	Right bundle branch block (8%)
I, II, aV_L	(complete and incomplete)
T wave (42%)	P pulmonale
Depression in V_1 to V_4 (50%)	Pseudoinfarction (16%)
	Conduction defects (AV block)
Axis Shift	
Pseudoinfarction (16%)	Right axis deviation (15%)
Left axis deviation	$S_1Q_3T_3$ (50%)
Clockwise rotation (16%)	Vertical rotation
S_1Q_3 (11%)	Q wave in aV_F
QS or QR in V_1	$S_1S_2S_3$ (16%)
Nonspecific Findings	
Sinus tachycardia (99%)	
Atrial arrhythmias (0% to 38%)	
With prior heart disease (38%)	
Without prior heart disease (4%)	
Transient low voltage	

AV = atrioventricular; S_1O_3 = significant S and Q waves in limb leads I and III, respectively; $S_1Q_3T_3$ = significant S and Q waves in addition to an inverted T wave in limb leads I, III and III, respectively; $S_1S_2S_3$ = significant S waves in limb leads I, II, III

*The numbers in parentheses are the percent association, when known. See text for references.

In case 1, electrocardiograms (Figure 1) showed significant interval changes, which were assumed (incorrectly) to be consistent with anterolateral infarction. In fact, the patient had atrial fibrillation (no P waves), transient right bundle branch block, clockwise rotation, anterior Q waves and a mild vertical plane axis shift, all consistent with massive pulmonary embolism. This patient showed an uncommon pattern of pseudoinfarction associated with massive pulmonary embolization described above. It should be emphasized that the original interpretation was not correct and that other possible explanations for the changes should have been entertained.

The electrocardiogram in case 2 (Figure 2) is an example of right ventricular strain (systolic overload) due to pulmonary embolism. Anterior and right precordial ST-segment elevation was misinterpreted as right ventricular ischemia/infarction and, consequently, pulmonary embolism was not considered.

In conclusion, we have presented two cases of massive pulmonary embolism simulating myocardial infarction and left ventricular dysfunction. Hemodynamic and electrocardiographic changes mimicking myocardial infarction obscured the correct diagnosis. These cases underscore the protean clinical manifestations of pulmonary embolization and reinforce the fact that scrutiny of all available data with special attention to clinical and electrocardiographic inconsistencies is critical for the correct diagnosis and appropriate therapy for this deadly masquerader.

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Atenolol Overdosage in a Patient With Progressive Renal Failure

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ATENOLOL (Tenormin, Stuart) is a relatively new, synthetic, β-selective adrenoreceptor-blocking agent. In contrast to most of the other drugs of its class, such as propranolol, which are relatively fat soluble and are primarily metabolized in the liver, atenolol is water soluble and is excreted by the kidney. Dosage reduction is therefore required when using atenolol in treating patients who have renal insufficiency.[1]

We report a case of atenolol overdosage due to renal failure that was successfully treated with continuous isoproterenol infusion.

Report of a Case

The patient, a 48-year-old man, had been in good health until six months before admission, at which time he noted the gradual onset of bilateral lower extremity paresthesia. Two months before admission, he was seen at another facility for gross hematuria. An intravenous ureterogram was normal and the patient underwent a three-week course of prednisone, 20 mg per day, which resulted in resolution of the hematuria.

(Giang DW, Isaeff DM: Atenolol overdosage in a patient with progressive renal failure. West J Med 1986 Jul; 145:101-103)

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The patient presented to the emergency department of another facility 18 days before admission complaining of the sudden onset of palpitations, chest pain, dyspnea and malaise. Cardiac monitoring documented atrial fibrillation with a ventricular response rate of 130 beats per minute. A total of 8 mg of verapamil was administered intravenously over 15 minutes, resulting in conversion to sinus rhythm at 80 beats per minute. On physical examination, no abnormalities were noted. Admission laboratory studies elicited the following values: blood urea nitrogen 43 mg per dl, creatinine 3.0 mg per dl, total protein 5.5 mg per dl and albumin 3.1 mg per dl. A urinalysis showed a specific gravity of 1.016, proteinuria (3+), hematuria (4+) and a sediment consisting of four to eight leukocytes, many erythrocytes, moderate amount of bacteria and zero to one casts (unspecified type). A myocardial infarction was ruled out by serial electrocardiograms and cardiac enzymes. Another intravenous ureterogram was normal. The Westergren sedimentation rate was 51 mm per hour. Results of further serologic and urine testing were nonspecific. The patient was given ampicillin, 500 mg every six hours orally, for the urinary tract infection; furosemide, 40 mg a day, and atenolol, 50 mg a day. He remained in normal sinus rhythm with a normal blood pressure.

On discharge and eight days before admission to our facility, the patient had a urea nitrogen level of 79 mg per dl and a creatinine level of 3.9 mg per dl. A regimen of atenolol, 50 mg a day, furosemide, 40 mg a day, and temazepam, 30 mg at bedtime, was dispensed.

The patient arranged to be admitted to Loma Linda University Medical Center for a second opinion concerning his renal problems. He continued to comply with his medication regimen. On the day before admission, the patient had two syncopal episodes on arising. Each lasted less than a minute, and they were not associated with chest pain, palpitations, aura, abnormal movements or a postictal state. By the day of admission, he could not even sit up in the car without orthostatic light-headedness.

On initial evaluation, the patient was found to have an apical pulse rate of 20 beats per minute and a blood pressure of 74/28 torr supine. The patient lost consciousness upon attempting to sit up in bed. He was placed in the Trendelenburg position and transported to the intensive coronary care unit, where cardiac monitoring showed complete heart block with a ventricular rate of 12 per minute (see Figure 1).

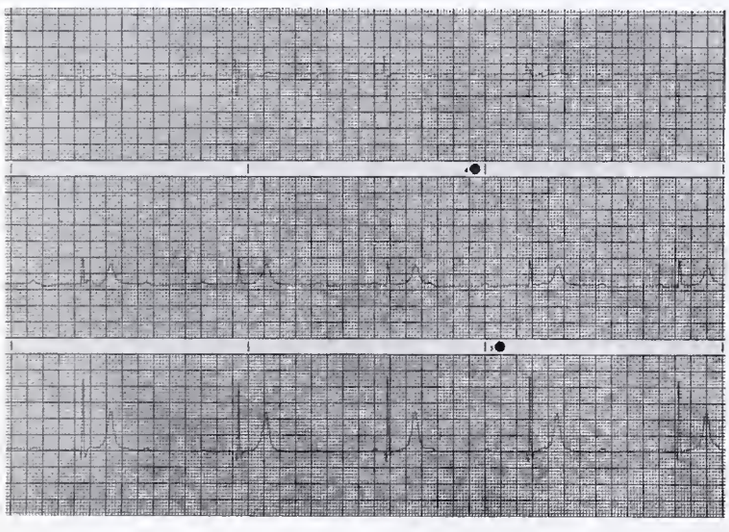

Figure 1.—Electrocardiographic rhythm strips taken at time of admission to the coronary care unit.

On physical examination he was noted to be diaphoretic and lethargic but responded to voice and was well oriented. No carotid bruits were heard. The lungs had fine bibasilar rales but no wheezing. Heart sounds were distant. There was a regular bradycardia with rare extra beats. There were no murmurs on auscultation. The abdomen showed no abnormalities and no organomegaly. The extremities were warm with weak pulses but without edema. There was no presacral edema.

Initially atropine sulfate was administered by intravenous bolus (a total of 1 mg over three minutes) without response. An intravenous infusion of isoproterenol hydrochloride (2 mg diluted in 250 ml of 5% dextrose solution) was begun at a rate of 3.3 μg per minute. The infusion rate was titrated upward rapidly until a clinical effect was noted with an infusion rate of 6.7 μg per minute. Eight minutes after initiating the isoproterenol infusion, the pulse was 46 per minute and the blood pressure was 104/20 torr. Intra-arterial peripheral blood pressure monitoring was instituted.

Laboratory studies done at admission (before treatment) elicited the following values: sodium 128, potassium 5.8, chloride 93 and carbon dixoide 21 mEq per liter; blood urea nitrogen 119, creatinine 6.9, total protein 5.1 and albumin 2.5 mg per dl; alkaline phosphatase 80, aspartate aminotransferase (formerly glutamic-oxaloacetic transaminase) 27 and alanine aminotransferase (formerly glutamic-pyruvic transaminase) 13 units per liter; lactate dehydrogenase 179 units per ml; calcium 2.0 mmol per liter, and phosphorus 2.9 mg per dl. The Westergren sedimentation rate was 121 mm per hour, the leukocyte count was 11,700 per μl with 82% segmented neutrophils, hemoglobin 9.2 grams per dl, hematocrit 27.4% with normochromic and normocytic indices and platelet count 332,000 per μl. Arterial blood gas measurements with the patient receiving 4 liters of oxygen per minute via nasal cannula showed a pH of 7.43, a partial carbon dioxide pressure of 29 torr, a partial oxygen pressure of 98 torr and bicarbonate 19 mEq per liter.

During the first four days in hospital, the patient was treated with an intravenous infusion of isoproterenol that was titrated to keep the mean arterial blood pressure above 60 torr. Infusion rates up to 8.7 μg per minute were necessary. He had no further syncopal episodes. Cardiac monitoring revealed variable second- and third-degree blocks. Temporary pacing was not required to maintain a satisfactory pulse rate and arterial pressure. Potassium-binding resin was administered to decrease the serum potassium level. The urea nitrogen and creatinine values improved without the use of dialytic therapy.

By the fourth hospital day, the patient had a pulse of 85 per minute and a blood pressure of 86/43 torr, and the isoproterenol dosage was tapered off. At that time, the urea nitrogen level was 93 mg per dl, the creatinine level was 3.9 mg per dl and the potassium value was 4.7 mEq per liter. Over the following two days, the patient had alternating atrial fibrillation and atrial flutter with ventricular response rates varying between 60 and 128 per minute. Digoxin was administered intravenously to control a rapid ventricular response and the patient converted to normal sinus rhythm on the seventh hospital day while undergoing a muscle biopsy under local anes-

thesia. At that time the urea nitrogen level was 65 mg per dl and the creatinine 2.8 mg per dl.

The patient's condition remained stable throughout the rest of the hospital stay. A 24-hour continuous electrocardiographic monitor on the 12th hospital day showed a normal sinus rhythm with a rate ranging between 72 and 110. An echocardiogram showed mild left atrial and left ventricular dilatation and normal left ventricular function. A percutaneous needle biopsy of the kidney showed crescentic glomerulonephritis. Prednisone therapy, 120 mg per day, was started, followed by a tapering regimen. After 33 days in hospital, the patient was discharged on a regimen of prednisone and hydrochlorothiazide. At discharge, the urea nitrogen level was 20 mg per dl and creatinine 1.8 mg per dl. Since discharge (18 months), the patient has remained asymptomatic, with a creatinine level of 1.5 mg per dl.

Discussion

A previous case of atenolol overdosage has been reported that involved the ingestion of 1,200 mg of atenolol during an attempted suicide by a 24-year-old woman under treatment for hypertension. The patient's pulse remained above 60 per minute and her blood pressure remained hypertensive. She was treated conservatively and no complications developed.[2] Another case was reported of a suicide attempt of a 22-year-old woman ingesting 1,000 mg of atenolol. The only electrocardiographic abnormality noted was frequent sinus pauses persisting for 34 hours postingestion but progressively decreasing in frequency during observation.[3]

In 1979 Frishman and co-workers reviewed the world literature on overdoses of β-adrenoreceptor-blocking agents. In all, 22 cases were reviewed. Bradycardia, hypotension, low cardiac output, cardiac failure and cardiogenic shock were reported as common complications. Bronchospasm, respiratory failure, seizures, hypoglycemia and eventual asystole were also reported. Atropine, 0.5 to 3.0 mg administered intravenously, was recommended as initial therapy, to be followed by isoproterenol infusion if atropine was not successful. Dobutamine and norepinephrine were also used. In a case wherein medical management fails to reverse bradycardia, a temporary pacemaker is required.[4]

In Frishman's second edition of *Clinical Pharmacology of the β-Adrenoceptor Blocking Drugs,* he has updated treatment that suggests the use of a selective β-adrenoreceptor agonist in treating overdosage with β_1-selective adrenoreceptor blocking agents.[5]

Other treatment modalities have been suggested for cases refractory to isoproterenol, including intravenous administration of glucagon[6] and calcium chloride.[7]

The patient in the case described here showed severe bradycardia and hypotension due to impaired renal clearance of atenolol and consequent excessive β-adrenoreceptor blockage. Indeed, atenolol may have exacerbated the renal failure by decreasing renal perfusion in this case.

Although no levels of atenolol were assayed, the constellation of symptoms suggests atenolol overdosage as the most likely cause. Neither temazepam nor furosemide have been reported to cause bradycardia, although both are known to cause hypotension and other symptoms reported by the patient.[8]

The patient did not manifest bronchospasm, although isoproterenol would tend to counteract this symptom. At no point was there evidence of congestive heart failure other than the slight bibasilar rales on admission. The patient responded dramatically to isoproterenol infusion but did not respond to intravenous administration of atropine. A temporary pacemaker was not required.

β-Adrenoreceptor-blocking agents are deactivated by the liver or kidney depending on their degree of water solubility. Propranolol, metoprolol tartrate, labetalol hydrochloride and timolol maleate are all relatively lipid soluble and are primarily metabolized in the liver. Contrariwise, atenolol and nadolol are relatively water soluble and are excreted by the kidney. Pindolol is intermediate.[9]

To avoid toxicity in the presence of impaired renal function, the manufacturer recommends reducing the dosage of atenolol according to the creatinine clearance: clearances greater than 35 ml per minute per 1.73 m^2 do not require adjustment; for clearances between 15 and 35 ml per minute per 1.73 m^2, 25 mg per day (or 50 mg every other day) is recommended.[10]

Although dosage reduction can be used to guide atenolol administration in patients with stable renal function, it seems prudent to substitute a lipid-soluble agent in patients whose renal state is changing rapidly and in whom β-adrenoreceptor blockage is required.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Rebound Hypertension Associated With Transdermal Clonidine and Contact Dermatitis

TO THE EDITOR: Transdermal clonidine has been reported to be effective in the control of mild to moderate hypertension.[1] The transdermal administration has been associated with contact dermatitis in 16% to 40% of patients. It has been stated that severe rebound hypertension secondary to clonidine withdrawal does not occur with the transdermal system.[2]

We recently encountered a patient in whom contact dermatitis to transdermal clonidine developed and who simultaneously presented with apparent rebound hypertension from clonidine withdrawal. The patient in question is a 67-year-old woman with a history of essential hypertension who had been maintained on a regimen of 20 mg of furosemide and 100 mg of atenolol per day given by mouth. Because of persistent blood pressures of 150/95 mm of mercury, transdermal clonidine (Catapres-TTS-2) was added to her regimen and her blood pressure was well controlled for 11 weeks. During that time her seated diastolic blood pressure averaged 86. In the tenth week, skin irritation occurred and early contact dermatitis was considered. Her blood pressure was 126/82 mm of mercury and her therapeutic regimen was maintained.

Six days later she presented with complaint of nausea, light headedness, global headache and painful pruritus at the site of the transdermal patch. Despite her symptoms, she had left the patch in place and it was found to be in firm contact with the skin. She was afebrile, her pulse was 60 and her seated blood pressure was 185/110 mm of mercury in both arms. Examination of the skin beneath the patch showed edema, erythema and vesiculization consistent with contact dermatitis. Her weight was unchanged and her renal function remained normal. The transdermal system was discontinued and the patient was started on a regimen of clonidine, 0.1 mg given by mouth twice a day. The furosemide and atenolol administration were continued. She was seen the next day, after the third dose of clonidine, and she was asymptomatic with a blood pressure of 120/88 mm of mercury.

It appears that these events are consistent with a clonidine withdrawal syndrome that was probably exacerbated by the coadministration of a β-blocker.[3] Since this occurred with the patch in place, but in the presence of contact dermatitis, we conclude that the clonidine was not absorbed secondary to the inflammation associated with a type IV allergic reaction. Theoretically, discontinuing the transdermal clonidine should lead to a slow taper of the drug because of a dermal drug reservoir. Our experience suggests that this theory may not apply when contact dermatitis to the system has developed.

We, therefore, recommend that patients who develop contact dermatitis to the transdermal clonidine patch system be observed for the onset of rebound hypertension. This recommendation particularly applies to patients who are also receiving a β-blocker.

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A Solution to Maizie's Problem?

TO THE EDITOR: In reference to the article entitled "Maizie's Problem" by E.R.W. Fox, MD, in the September 1985 issue,[1] I have chanced upon a simple and natural solution to the problem of flatulence after eating beans. A relative of mine introduced my family to baked beans rendered free of their tendency to gastrointestinal upset by the addition of chunks of pineapple included before baking. My wife used this ingredient to prepare what we have since dubbed "Hawaiian chili" simply by adding chunks of pineapple to her chili recipe. The pineapple does not affect the flavor of the chili but results in a main course that meets with maintenance of gastrointestinal equanimity.

I am uncertain of the chemical reactions involved; however, it would seem a much more simple approach than to expose the beans to radiation.

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What Caused the Plague of Athens?

TO THE EDITOR: In Dr Ganem's excellent article "Plasmids and Pestilence" in the April issue,[1] he identified, without doubt, the Athenian plague of the Peloponnesian Wars as having been bubonic plague. Medical historians have been less sure of that diagnosis. Hans Zinsser in his classic "Rats, Lice and History"[2] devoted more than seven pages to a differential diagnosis based on a careful study of the description in the second book of the history of Thucydides. While he considered bubonic plague and typhus in his differential diagnosis, he concluded that smallpox best reflected the description of the Greek historian.

In a more recent analysis, Langmuir and colleagues invoked a dual epidemic of influenza and toxigenic staphylococci.[3] Even that was questioned by Morens and Chu who blamed Rift Valley fever.[4]

Despite the sexual orientation of many Athenian and Spartan men at that time, one may be certain that the epidemic was not AIDS.

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Cognitive Dissonance

To the Editor: A new disease has struck among surgical patients. It causes delay and postponement of timely surgery which extends the discomfort and disability of the disease that indicates surgery and increases the magnitude of the surgery ultimately required to control the disease. It is spread by third party payers.

The disease is *cognitive dissonance*, a term borrowed from the commercial literature. Another common term is "buyers remorse." The vector is the mandatory second opinion program which twists a time-honored feature of high-quality medical care into an instrument of parsimony. The pathways create a series of administrative hurdles which must be negotiated by apprehensive patients in whom is implanted the notion that any surgeon who would propose *this* operation should be automatically questioned. Inevitably, the process leads to speculation whether such a surgeon should be entrusted to *any* extent with one's life and well-being.

Many centers are working on finding a cure. Once again, those who primarily focus on finances in preference to quality of outcome will be favored by the selection afforded by this disease.

With the best of intentions, the rules of medicine have again been altered to favor the mendacious rather than the caring.

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California Legislation to Inform Patients

To the Editor: Regarding your editorial "How About Some Affirmative Action for Patient Advocacy?" in the April issue,[1] I believe that the readers of the journal should be aware that efforts are being made in the interest of our patients. One of the greatest threats to the role of physicians as patients' advocates are those systems of health-care delivery that utilize the gatekeeper concept. Those physicians who act as gatekeepers clearly must align themselves with the interests of the health maintenance organization (HMO) that employs them. At times, this means the restriction of health-care services, even when others may attest to the need for such services. Unfortunately, many slick marketing techniques fail to inform those persons who enroll in such systems that they may lose their free choice of physician. To this end, the California Congress of Dermatological Societies proposed a resolution which the California Medical Association House of Delegates passed and which has since been proposed as California Assembly Bill 2967. As introduced it would have required that any descriptive material used by health-care delivery systems must prominently include a statement advising that participation in such plans will restrict the free choice of physician and hospital. Now amended, it would call the attention of prospective enrollees to detailed materials that clearly describe how the plan would affect choice of physician.

We physicians must do all we can to help our patients. This bill may be just the sort of advocacy that the editorial referred to. If other readers in California are in favor of it, I hope that they contact their legislators.

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REFERENCE

1. Watts MSM: How about some affirmative action for patient advocacy? (Editorial). West J Med 1986 Apr; 144:458

Patient Advocacy

To the Editor: Your editorial on patient advocacy in the April issue[1] addresses a most important and strangely neglected subject. In this area of patient representation there is a conspicuous void.

I have recently written an "educational" letter to my patients about some of the ongoing and proposed changes in medical care (insurance) programs. The response was quite strong. But when patients ask me who there is to represent their needs in formulating these new programs, I don't know how to answer. Many patients are most anxious to support any advocates who will try to protect their health and preserve and improve their health care; but where are these advocates? They speak up with silence.

Legislators are not interested now in improving health care programs, but only in lowering costs. Physicians in practice, involved in direct patient care and trying to survive the economics of the new plans, are very little involved in the design of these new plans to serve patients. Organized medicine seems to have its hands full helping its member physicians, not acting as patient advocates.

Must lowering costs mean ignoring patients' medical care needs? Not completely. But few doctors, or very many others who represent patients and understand their medical requirements, are involved in designing the lower cost programs, with service to and protection of individual patients in mind. Individual physicians may make heroic efforts to protect individual patients from being hurt by a particular administrative "crack" in a single insurance plan. This will help very little, in spite of all the effort. The insurance plan itself must be changed. Physicians who know how to take care of patients must act as consultants as all these new plans are developed and revised. This is certainly not done presently.

Ours is a noble profession. Economic pressures must not divert our attention from the health of our public. We also cannot survive if we use our resources only to protect ourselves rather than to provide care for our patients.

A large job needs to be done. There are extra physicians around everywhere. Let's get busy.

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REFERENCE

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Topics in Primary Care Medicine

Evaluation of Impotence

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

Impotence is a prevalent and distressing problem. Not infrequently, impotence is a symptom of a medical disease or a side effect of drug therapy. The proper management of a case of impotence requires, besides technical medical competence, understanding the patient's important relationships and his attitudes towards sexuality. Finally, impotence is an interdisciplinary problem. A comprehensive initial evaluation should be undertaken by the primary practitioner before consultation with an endocrinologist, urologist, vascular surgeon or sex therapist if inappropriate referrals are to be avoided.

Prevalence and Underdiagnosis

Impotence, defined as a failure to achieve an erection adequate for intercourse in 25% or more of attempts, increases with advancing age. At age 40, about 1.5% of otherwise healthy men have impotence. At age 60, the prevalence increases to 10% to 25%, and at age 70 to 30% to 55%. Impotence in an elderly man, however, should not be accepted as normal by a physician any more than one would accept the development of cataracts. The overall prevalence of impotence in adult men with medical problems is between 10% and 35%. It is likely more common in medical clinic patients than in healthy men, but age-matched data are difficult to find. The prevalence of impotence clearly depends on the population examined. In populations with a high prevalence of diabetes mellitus, other endocrine disorders or vascular disease, more impotence will be found. However, in a study of consecutively questioned patients in the general medical clinic at the Minneapolis Veterans Administration (VA) Medical Center, the prevalence of impotence was 34%. Even more remarkable, only 1.5% of patients who complained of impotence as conventionally defined had discussed it with their physicians. Undoubtedly several factors contribute to the underdiagnosis of impotence by primary physicians. Patients are often tentative in their initial complaint and may use idioms to describe sexual dysfunction that are unfamiliar to their physicians. Conversely, in reviewing systems, a physician may use terminology that is unfamiliar to the patient and fail to elicit the complaint. Finally, feeling that impotence is generally psychogenic and therefore outside his or her expertise, a physician may not ask after the difficulty at all.

Pathophysiology

A brief review of male sexual physiology is useful in understanding the medical, psychologic and pharmacologic conditions associated with impotence. The components of male sexual performance are libido, erection, emission, ejaculation and orgasm. The mechanisms by which specific diseases interfere with sexual function are listed in Table 1.

Libido, or desire for sexual intercourse, is cortically mediated. Testosterone plays a permissive role but is clearly insufficient alone. Conditions that interfere with a normal libido include all degrees of psychologic disturbance, from stress following an argument to major psychiatric illness. Endocrine conditions, particularly primary and secondary hypogonadism, thyroid dysfunction, Cushing's disease and prolactinoma, also impair libido. Finally, poor general health and the presence of serious medical disorders which limit stamina also quite typically affect libido. It should be noted, however, that our culture attaches such importance to a vigorous libido that many patients with a serious endocrinopathy or psychological disorder will state that their interest in intercourse is unaffected and that the primary problem is erectile dysfunction. Therefore, the stated presence of a normal libido should not be taken to exclude these cortically mediated problems.

Erection is a complex phenomenon in which two separate nervous centers participate. In addition, the process requires adequate blood flow and normal erectile structures in the penis. The cortical erectile center appears to be located in the limbic brain and to be a dopaminergic system. Its outflow, which is α-adrenergic, is at the T-12 to L-2 spinal cord level. The function of the cortical erectile center may be impaired by

(Cooke M: Evaluation of impotence. West J Med 1986 Jul; 145:106-110)

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thoracic spinal cord lesions and by anatomic or pharmacologic interference with the sympathetic nervous system. The second erectile center, the reflexogenic center, is located at L-2 to L-4 and is a part of a parasympathetic spinal cord reflex loop. Trauma and surgical repair of the sacral cord may result in impotence through ablation of the reflexogenic erectile center. Anticholinergic agents, including antihistamines and antidepressant and antipsychotic agents, may produce a pharmacologic parasympathectomy and impotence. Antihypertensive drugs that act through ganglionic blockade probably interfere with sexual function in this manner as well. Pelvic fractures and extensive pelvic surgical repair can cause impotence if the pelvic plexus is disrupted. Vascular insufficiency resulting in impotence usually reflects extensive atherosclerosis and may cause a classic Leriche's syndrome, although impotence may be present without claudication. Occasionally vascular insufficiency reflects a surgical accident or posttraumatic anatomy. Impotence develops in 30% to 50% of men with diabetes mellitus; a proportion appears to result from diabetic macrovascular complications as well as from autonomic neuropathy. Mechanical disorders of the penis prevent a normal erection while inflammatory conditions such as balanitis, urethritis and prostatitis may cause pain and secondarily impotence. Impotence is a common complication of recurrent priapism.

Emission—the delivery of semen into the proximal urethra and closure of the internal vesical sphincter—and ejaculation are primarily sympathetically mediated processes, in contrast to the parasympathetic control of erection. Traumatic and anatomic disruption of the sympathetic nervous system, such as pelvic node dissection and lumbar sympathectomy, and the use of sympatholytic drugs, may result in impotence. Retrograde ejaculation is the sexual dysfunction that particularly reflects the loss of α-adrenergic input.

Orgasm is the least understood component of male sexual performance. It appears to be cortically mediated. The reports of patients with spinal cord injuries and certain elderly men with erectile dysfunction suggest that orgasm can be experienced independent of erection and ejaculation.

The Relative Importance of Organic and Psychogenic Factors

It would be of great use to clinicians to know the relative prevalence of the causes of impotence. It is commonly stated that 90% of impotence is psychogenic. There are no data to support this assertion, however. Available data reflect the epidemiology of self-selected patients and patients referred to subspecialty clinics and may not be generalizable to primary care (Table 2). It is important to note that the Minneapolis VA study, which was relatively free of subspecialty bias, showed a preponderance of organic causes. In this study, of the 401 screened men who admitted impotence, 188 elected to have further workup. Patients declining workup tended to be slightly older, with more medical diagnoses and medications. Of the 188 men who underwent evaluation, 80% were found to have impotence on an organic basis, while 14% were felt to have psychogenic impotence. Of the evaluated group, 38% had endocrine disease, particularly primary and secondary hypogonadism, hypothyroidism, hyperthyroidism and prolactinomas, and 25% had a medication side effect as the underlying cause of impotence. Thus, while no study definitively establishes the relative importance of the various causes of impotence, it is clearly erroneous to assume that impotence always has a psychogenic cause. Upwards of half of all cases may reflect organic difficulties, particularly endocrine disease and medication side effects.

Evaluation of a Patient With Impotence

The first step in the evaluation of impotence is to establish that the symptom is present. A physician must be alert to

TABLE 1.—*Components of Male Sexual Response and Mechanisms of Impotence*

Response	*Physiology*	*Disorders Causing Impotence*
Libido	Cortical, testosterone required	Psychic: fatigue, stress, performance anxiety, depression, relationship disturbance, profound psychiatric disorders
		Sedation and sedative abuse
		Endocrine disease: testosterone deficiency, elevated prolactin, thyroid disease
		Poor general health
Erection	Cortical erectile center, sympathetic outflow at T-12 to L-2	Diseases of limbic system
		Cord injuries and diseases: transection above T-11 (90% have reflexogenic erection), multiple sclerosis, tabes
		Sympathetic neuropathies: surgical—aortoiliac bypass, lumbar sympathectomy, node dissection, AP resection of rectum; pharmacologic—sympatholytic antihypertensives, α-blockers including phenothiazines
	Reflexogenic erectile center, parasympathetic spinal reflex S-1 to S-4	Cord injuries and diseases: destruction of sacral cord (20% have cortical erections)
		Parasympathetic neuropathies: surgical—AP resection of the rectum; pharmacologic—anticholinergics, antidepressants, antihistamines, antipsychotics
	Vascular supply and normal erectile tissue	Vascular diseases: atherosclerosis, trauma
		Penile diseases: Peyronie's disease, chordee, microphallus, priapism
Emission and ejaculation	Sympathetic thoracolumbar reflex	Sympathetic neuropathies: surgical, as in cortical erectile center dysfunction; pharmacologic, especially guanethidine, thioridazine hydrochloride
Orgasm	Cortically mediated, independent of erection and ejaculation	

AP = anteroposterior

TABLE 2.—*Effect of the Study Population on the Relative Prevalence of the Various Causes of Impotence*

Cause of Impotence	Study Populations: 105 Patients in Whom a Serum Testosterone Level Was Measured,* Percent	188 General Medical Patients Undergoing Evaluation,† Percent	165 Patients Referred to Urology Clinic,‡ Percent
Psychogenic	14	14	51
Organic	66	80	47
Medication	7	25	2
Alcohol	3	0	1
Neurologic (excluding diabetes)	0	7	4
Vascular/penile	0	6	15
Endocrine	51	38	25
Primary and secondary hypogonadism	26	19	25
Diabetes	7	9	...
Other: thyroid prolactin	18	10	...
Miscellaneous	5	4	9
Mixed/unknown	19	7	2

*Spark RF et al (JAMA 1980; 243:750-755).
†Slag MF et al (JAMA 1983; 249:1736-1740).
‡Montague DK et al (Urology 1979; 14:545-548).

tentative comments by the patient about this intimate topic. The use of concrete description and lay terminology is often more productive in eliciting the complaint during a review of symptoms than the use of medical terms. Once it has been established that the patient suffers from impotence, the goal of the evaluation is to uncover the cause. Because many organic causes of impotence are not associated with a hormonal disruption, it should not be assumed that all impotence occurring in patients with a normal testosterone level is psychogenic. The evaluation should instead proceed in an orderly manner. The interview should permit clarification of the sexual problem, documentation of the general sexual history and evaluation of the relationship in which the dysfunction is occurring. This can be accomplished and a directed physical examination done in three brief visits, as shown in Table 3. None of the visits need devote more than 15 minutes to discussing the sexual dysfunction; the workup can thus be accommodated within a busy clinic schedule. If the patient and physician are well known to one another, there may be little barrier to discussing sexual function and the evaluation can proceed even more expeditiously.

TABLE 3.—*Three-Visit Assessment of a Patient With Impotence*

- First Visit
  - Patient's narration
  - Physician-directed clarification
  - Review for presence of general medical problems and depression
  - Patient's view of the problem
  - Initial assessment and plan
- Second Visit
  - Patient's review of the problem
  - General sexual history
  - Physical examination: vascular, neurologic, genital
  - Assessment and plan
- Third Visit
  - Patient introduces sexual partner
  - Partner's view of the problem
  - Assessment of health of relationship and communication skills
  - Assessment and plan—decision regarding laboratory workup and/or referral

The first visit is devoted in large part to the patient's narration of his symptom history. There are typically very strong feelings attached to this problem; having established that the physician is comfortable with the subject matter, patients are often eager to describe the difficulties they have. After an initial unstructured and patient-directed history, the physician should ask about the onset and the emotional setting of the initial episodes of impotence, current level of libido and presence or absence of morning erections. Patients should be asked about the number of sexual partners and whether impotence occurs uniformly or is restricted to a particular consort. A brief review of symptoms to screen for depression and general medical, endocrine and vascular diseases should be undertaken. In addition, the patient should be questioned about alcohol, prescription drug, over-the-counter and illicit drug use. Numerous drugs are associated with impotence by a variety of mechanisms (Table 4); antihypertensive drugs are a particularly troublesome cause of iatrogenic impotence. The reported prevalence of erectile disorders in patients on antihypertensive therapy is listed in Table 5. It may be useful to ask the patient why he thinks he has the difficulty; this information provides both useful diagnostic clues and insight into the symbolic value of the dysfunction for the patient. Finally, the physician should close with a provisional assessment and explanation to the patient of the next step.

At the second visit the patient is given an opportunity to review the problem and, not uncommonly, will add new or different information. At this time, the general sexual history, which may seem intrusive to the patient at the time of the first visit, can be obtained. A directed physical examination is made, noting in particular general medical condition, evidence of endocrine dysfunction, autonomic neuropathies and vascular insufficiency. On genital examination, the testicles, prostate and phallus are assessed. Evidence of testicular atrophy, microphallus, the corporeal plaques of Peyronie's dis-

TABLE 4.—*Commonly Used Drugs Associated With Impotence and Postulated Mechanism of Action*

Sexual Response	*Mechanism of Action*	*Drugs*
Libido	Sedation	Antihypertensives: methyldopa, reserpine, clonidine, β-antagonists; alcohol; narcotics; minor tranquilizers, barbiturates; phenothiazines; baclofen
	Testosterone antagonism	Alcohol, marijuana, spironolactone, cimetidine, estrogen, digoxin
	Elevation of prolactin	Narcotics, phenothiazines, methyldopa
Erection	Parasympatholysis	Atropine, benztropine, propantheline; disopyramide, metoclopramide; antidepressants, especially amitriptyline; antipsychotics, especially chlorpromazine and thioridazine; antiparkinsonian drugs/antihistamines
Ejaculation	Sympatholysis	Antihypertensives: guanethidine, phenoxybenzamine, prazosin; monoamine oxidase inhibitors; antipsychotics, especially thioridazine

TABLE 5.—*Estimated Prevalence of Impotence Associated With Antihypertensive Therapy**

Antihypertensive Therapy	*Percent*
Untreated (receiving placebo)	10
Diuretic—thiazide	19
β-Blocker—propranolol	15
Centrally active agents—	
guanethidine	60
reserpine	30
clonidine	24
methyldopa	30
prazosin	†
Vasodilators—	
hydralazine	Occasional
minoxidil	Rare
captopril	Occasional

*Prevalence is expressed as percentage for convenience, although the number of subjects on which these percentages are based is often quite small.
†Rarely reported but common in clinical practice, especially at higher doses.

ease, phimosis, balanitis and prostatic disease is particularly sought. This session should again close with a statement by the physician indicating his or her working assessment and plan for the next step.

The third visit should include the regular sexual partner if the patient is willing. During this visit, the partner's view of the difficulty can be presented. As the physician explores the difficulty with the couple, it is important to make an initial assessment of the health of the relationship and the ability of the partners to communicate about sexual matters. There is often an opportunity to provide education and correct misconceptions. This visit also closes with the statement of the physician's assessment of the problem and plans for a further evaluation, including laboratory tests and consultation.

Often a three-visit evaluation as described above will be enough to clarify the mechanism of impotence (Figure 1). When impotence is due to psychological causes, the relative importance of performance anxiety, minor disturbances and

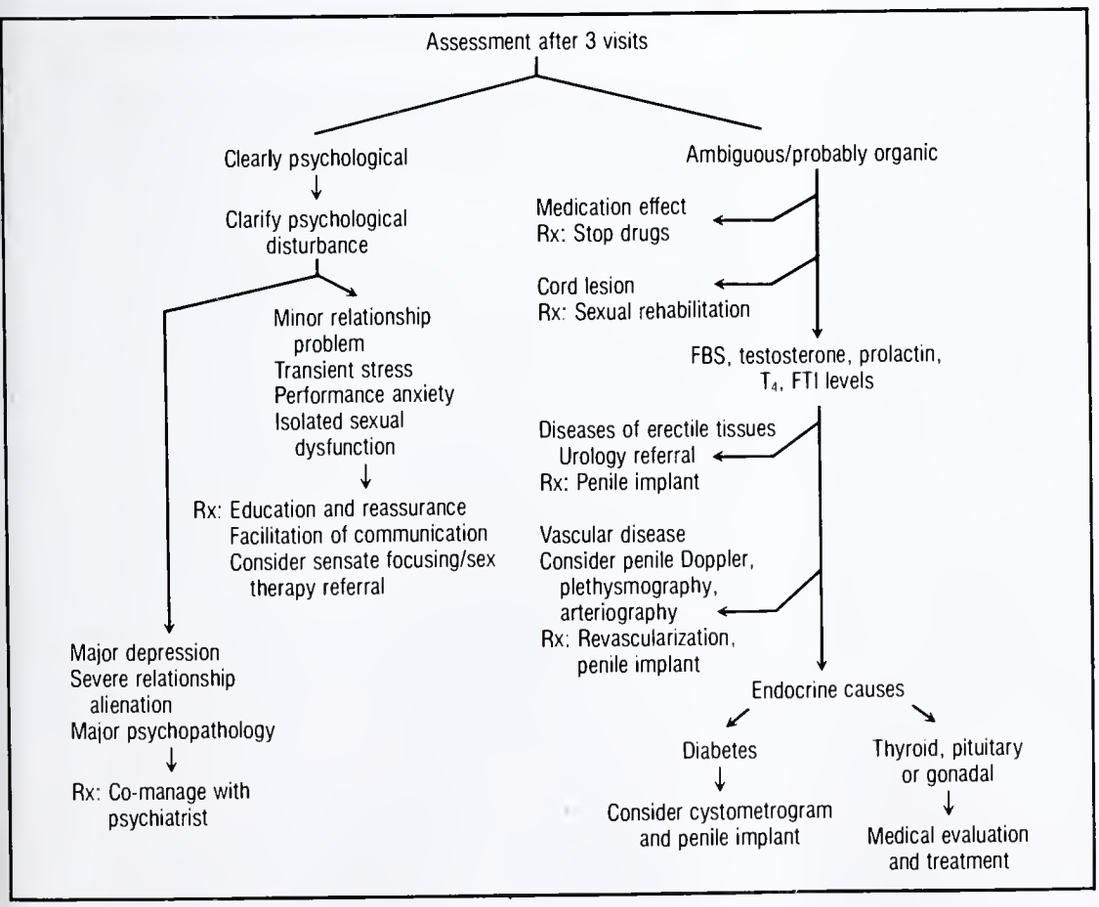

Figure 1.—Further evaluation of a man with impotence. FBS = fasting blood sugar, FTI = free thyroxine index, T_4 = thyroxine

major intrapsychic or interpersonal disorders should be estimated. Men whose impotence is related to fatigue or stress that can be expected to be brief in duration will usually require only an explanation of the phenomenon and reassurance. Couples in fundamentally healthy relationships who have poor communication skills may benefit from more formal sex therapy, possibly including sensate focusing. More profound disturbances, including gender misidentification, severe depression, psychotic disorders and profound relationship alienation, are appropriately managed in consultation with a psychiatrist.

In situations in which impotence is not unequivocally psychogenic, evaluation to exclude organic causes is appropriate, as reassurance, sex therapy and psychiatric consultation cannot be expected to fully address the problem. If therapeutic or recreational drug use may be contributing, the response to a drug-free period, if feasible, should be evaluated before laboratory evaluation and referral. Men who are abusers of alcohol can be expected to recover sexual function when abstinent, if a physical examination does not show testicular atrophy, palmar erythema, spider angiomata or other signs of estrogenization. Patients in whom cord injury, a cord operation or spinal cord disease is causing impotence may benefit from sexual rehabilitation techniques. Patients in whom a psychogenic, spinal cord or drug-induced cause is not apparent should have determination of serum prolactin, thyroxine, thyroid-stimulating hormone, serum testosterone and random blood glucose levels. The use of nocturnal penile tumescence testing is unnecessary and may be misleading, as partial tumescence without turgidity adequate for intercourse may occur in a patient with organic impotence. If a low serum testosterone level is found, primary gonadal failure should be distinguished from pituitary disease by determining serum luteinizing and follicle-stimulating hormone levels. Impotence associated with thyroid disease resolves with the treatment of the primary disorder. Impotence associated with diabetes may be helped by a penile prosthesis. If results of these studies are normal, vascular or penile disease may be the cause of impotence. Determination of the brachial-penile blood pressure ratio and arteriography permit identification of macrovascular disease but a bypass operation is rarely successful in correcting vaseulogenic impotence. Rather, these patients should be referred to a urologist and considered for a penile implant. Preliminary experience with the intracavernosal injection of papaverine combined with duplex Doppler scanning of the penile artery suggests that this technique is useful in distinguishing patients with severe arterial insufficiency from those with endocrine, hormonal and psychogenic impotenee and in predicting the response to yohimbine, an oral vasodilator. Urologic consultation is also appropriate in those in whom a general evaluation had shown disease of the erectile tissues.

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Public Health and Preventive Medicine

Smokeless Tobacco—An Overview for Physicians

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This is one of a series of articles from western state public health departments.

The cliché "history repeats itself" is all too true in the case of tobacco. While we are successfully reducing the prevalence of smoking, there is a resurgence in the use of smokeless tobacco. Dipping snuff and chewing tobacco are practices that have existed for centuries. Smokeless tobacco use faded after the invention of the cigarette-making machine in 1881, but such use is climbing dramatically into popularity again.

During the 17th and 18th centuries, snuff was the preferred mode of tobacco use in England. Snuff taking became an integral part of fashionable life in England and was openly practiced by both sexes.[1,2] By the mid-1700s, a man who did not take snuff was not considered a gentleman. Ladies took snuff as "artistically, vigorously and conspicuously as men and the method of taking snuff and the ritual of opening and tapping the box were reduced to a fine art."[1] Snuff also acquired a reputation as a powerful disinfectant and preventive agent against the plague.[1]

During the 1800s, tobacco chewing became known as "the American habit."[1] A communal snuff-box and cuspidors were installed for members of Congress, a practice that continued until the mid-1930s.[3] Maintaining spittoons cost taxpayers $400 a year.

Public outcry against unsanitary practices in the United States caused tobacco spitting to become socially unacceptable *and* unlawful in many public places. This factor, combined with the inexpensive mass production and successful marketing of cigarettes, led to a rapid decline in smokeless tobacco use. That decline has been reversed. Smokeless tobacco use has been on the increase since the early 1970s. Product sales have increased about 11% each year since 1974.[1] Much of the resurgence of smokeless tobacco can be attributed to a desire to use tobacco but to avoid the harmful effects of smoking.

The same skillful advertising techniques that have been used in the marketing of cigarettes are now used to promote smokeless tobacco products. Celebrities from many different sports are featured in smokeless tobacco ads. Youth-oriented movies portray "modern" cowboys or other "macho" characters who use smokeless tobacco as part of the tough-guy image.

One prime target area for the smokeless tobacco market is the American Southwest.[4,5] The Smokeless Tobacco Council claims advertisements are only used to create brand loyalty.[5] If that were true, the ads would concentrate on the quality of one product versus another, rather than promoting the image of the user. Instead, most smokeless tobacco ads contain a segment that shows a neophyte customer how to use the product. The US Tobacco Company Chair and President, Louis Bantle, estimated 80% to 85% of his company's customers were new users.[6] It is estimated that $10.2 million was spent in 1981 for promoting smokeless tobacco products, primarily through television and other broadcast media.[6]

Apparently the ads have been successful. While per capita sales of cigarettes have been on the decline, smokeless tobacco sales have increased. Estimates of current smokeless tobacco users range from 7 to 22 million nationally.[5,7,8]

Youth Prevalence

A survey conducted by the Utah Department of Health in late 1984 in five Utah public schools showed that 5% of 1,943 high school students used smokeless tobacco products during the past 24 hours and 8% used them during the previous week. Among male students, the figures were higher: 10% and 15%, respectively.

Smokeless tobacco use appears to be a social behavior. According to the National Institute on Drug Abuse, a strong relationship exists between an adolescent's chewing behavior and the chewing behavior of his or her friends.[9] This relationship was also seen in the Utah survey: 79% of the students who indicated having used a smokeless tobacco product within the previous 24 hours also reported that at least one of his or her two best friends was a user. Conversely, only 9% of those who reported never having used the products reported having a best friend who was a user.

(Dandoy S, Edwards G, Lindsay G: Smokeless tobacco—An overview for physicians. West J Med 1986 Jul; 145:111-113)

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Reprint requests to Gary L. Edwards, MS, Coordinator, Tobacco Risk Reduction Program, Utah Department of Health, PO Box 16700, Salt Lake City, UT 84116-0700.

Regular users (use in last 24 hours) and frequent users (use in previous week) were also more likely to report "purchase" as their method of procuring smokeless tobacco (63% and 45%, respectively). Such purchase is a violation of Utah's law restricting sale to those older than 19 years. Students appeared to begin experimenting with smokeless tobacco at a younger age (10.5 years) than with cigarettes (11.1 years). No significant differences in use were found between urban and rural areas.

Health Effects

The National Cancer Institute, World Health Organization, American Academy of Pediatrics, American Health Foundation and American Dental Association have accumulated a substantial body of evidence indicating that smokeless tobacco use increases the risk of oral cancer in humans. In fact, recent reports from the International Agency for Research on Cancer state that there is sufficient evidence to conclude that the oral use of snuff causes cancer in humans.[10,11] The first report linking the use of tobacco to cancer was published more than 200 years ago and described two patients with nasal cancer, both heavy users of snuff.[2] Since that time, more than 600 documented cases of oral, pharyngeal or laryngeal cancer directly linked to smokeless tobacco use have been reported in North American medical and dental journals.[8] One very unusual case of cancer directly linked to the use of snuff was reported by Root[12]: squamous-cell carcinoma of the concha of the left ear developed in a 58-year-old Minnesota farmer subsequent to his placing snuff in that ear daily to weekly for 42 years.

The most frequently cited epidemiologic study on the relation of smokeless tobacco to oral cancer was conducted by Winn and co-workers.[13] This case-control study in North Carolina involved 255 women with oral and pharyngeal cancer and 502 controls. The study showed that women who used snuff had a fourfold increased risk of oral and pharyngeal cancer than those women who never used tobacco in any form. Most striking were the risks associated with cancers arising in the tissues in direct contact with snuff, the cheek and gum. For those subjects who had used snuff for 1 to 24 years the risk was 13-fold. The risk rose to 50-fold for those who had used snuff for 50 years or more. Detailed analyses revealed that no other patient characteristics altered the risks associated with snuff use.

Carcinogens found in smokeless tobacco include polonium (a known radioactive α-emitter and radiation carcinogen) and two classes of powerful chemical carcinogens: polycyclic aromatic hydrocarbons and the nitrosamines. The most highly concentrated carcinogenic agents found in smokeless tobacco, however, are the tobacco-specific nitrosamines (formed from the tobacco alkaloids during processing).[14] The federal government has established strict levels for human exposure to certain nitrosamines in many consumer products—that is, 10 ppb total volatile nitrosamines in baby bottle nipples and 5 ppb in cured meats.[15,16] However, the concentrations of the four most common tobacco-specific nitrosamines in the five most popular brands of US snuff range from 9,600 ppb to 289,000 ppb.[10] Of particular interest is the finding that the levels of these nitrosamines in smokeless tobacco far exceed levels in other tobacco products.[11,14,17]

In addition to its relationship to cancer, smokeless tobacco appears to play a role in other areas of human health. Nicotine exposure in the habitual smokeless tobacco user is similar in magnitude to that of the cigarette smoker.[18] Although the cardiovascular effects of smokeless tobacco have not been studied in great detail, some information has been reported in the literature. In one study conducted by Squires and colleagues,[19] significant increases in heart rate and blood pressure were reported in 20 subjects given a 2.5-gram dose of smokeless tobacco. In a separate study, Schroeder and Chen reported "a direct and positive relation between smokeless tobacco use and higher blood pressure readings, particularly among young men aged 18 to 25."[20]

Of related concern is the sodium content of smokeless tobacco products. Hampson analyzed 16 retail brands of smokeless tobacco for sodium content.[21] The mean sodium content was found to be 1.76% by weight compared to such foods as dill pickles (1.43%) and cured, fried bacon (1.09%). The latter two items traditionally are considered high in sodium. Other health effects of smokeless tobacco products include hyperkeratosis, gingivitis, gingival recession, tooth abrasion, leukoplakia and nicotine addiction.[7,22-26]

An additional hazard of smokeless tobacco use may be its tendency to encourage and hasten cigarette smoking among young persons. In our survey of high school students, 72.1% of the students who reported using smokeless tobacco at least once also reported smoking at least one cigarette. Only 14.2% of those who reported never using smokeless tobacco had smoked one or more cigarettes. Robert N. Hoover, MD, of the National Cancer Institute has suggested that snuff users may switch to the more socially approved cigarettes as they become adults because adult society does not approve of smokeless tobacco use.[27] If this is true, the most dangerous aspect of smokeless tobacco use may be its role in promoting a behavior proved to cause heart and lung disease, cancer and a wide variety of other ailments.

Interventions

The reduced prevalence of adult male smoking has resulted from the combined educational efforts of individual physicians, public health agencies and voluntary health organizations. The first step in this national antismoking effort was to provide the public with information regarding the dangers of smoking. Although knowledge by itself may not produce behavior change, it is a necessary component. Currently the public does not have adequate information on the risks of smokeless tobacco.

Physicians must begin by dispelling the myth that smokeless tobacco is a benign and safe alternative to smoking. The US Surgeon General has stated that a very effective way to reduce cigarette smoking is for physicians to give clear and simple messages to their patients.[17] The ability of physicians and dentists to reduce smokeless tobacco use should be equally potent. Physicians should look particularly for signs of smokeless tobacco use in high-risk subgroups of the population. Counseling and education can be initiated by simply informing a patient that snuff-related lesions are apparent. Then the patient should be asked what he or she knows about the health consequences of smokeless tobacco use. The physician should fill in any gaps in the patient's understanding

by discussing leukoplakia, oral cancer and periodontal disease.[28] Telling patients that smokeless tobacco use may cause cancer or receding gums is less effective than explaining *how* it is doing so in the mouth of the patient. Such counseling is extremely simple, yet can be very effective. Subsequent visits by the patient should include follow-up counseling sessions concerning tobacco use.

Physicians and other health care providers must never underestimate their ability to promote behavior change in their patients. Schools of medicine, dentistry and nursing should assist students by providing specific instruction on counseling the smokeless tobacco user and the cigarette smoker.

Physicians have the additional role of providing leadership for collective societal interventions. Individual physicians and state and county medical associations should encourage governmental agencies to reduce the smokeless tobacco problem by increasing excise taxes, restricting sales to minors and banning advertisements which create the false impressions that smokeless tobacco use is "macho" and totally safe.

Requiring prudent warning labels is an additional deterrent strategy. Massachusetts recently required all snuff sold in that state to carry the label "Warning: Use of snuff can be addictive and can cause mouth cancer and other mouth diseases."[26] The fear that each state may enact legislation requiring similar warning labels may be one reason the smokeless tobacco industry is supporting warning label legislation on the federal level.

Future Research

There is still much to learn about smokeless tobacco. Future research must clarify the relationship between adolescent smokeless tobacco use and cigarette smoking. Public health officials should determine if the effective components of smoking cessation and school-based smoking prevention programs are as effective in dealing with smokeless tobacco. There is a need to determine the public's current perceptions of the risks and perceived benefits of smokeless tobacco. The impact of smokeless tobacco advertising on youth should be documented. Long-range prospective studies could strengthen causal links between smokeless tobacco use and cancer and periodontal disease.

Such prospective analyses take time and will not be available for many years. In the meantime, the evidence is strong enough for the medical community to make confident statements regarding the dangers of smokeless tobacco use. Our national experience with smoking suggests volumes of scientific data concerning the harmful effects of smokeless tobacco will begin accumulating rapidly now that we have sufficient reason for concern. We know enough now to warn patients of specific risks associated with smokeless tobacco products.

Effective health education programs seek to influence social norms as well as individual behaviors. The history of cigarette use shows that it becomes more difficult to change unhealthy behaviors once they become acceptable norms for large portions of the population. Based on burgeoning smokeless tobacco sales in the past decade, it is apparent that the longer the medical community waits before addressing this issue, the more difficult will be the battle. The time to act is now.

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The Arizona Health Care Cost Containment System

A Prepayment Model for a National Health Service?

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The Arizona Health Care Cost Containment System (AHCCCS), the Arizona Medicaid alternative, is an experiment in contracting "prepaid" indigent health care to the lowest bidding group. The consequences have been substantial cost overruns and serious unanswered questions about the quality and availability of care.

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Arizona was the last state in the union to be without a Medicaid program. Indigent health care was the responsibility of the counties, which were carrying increasingly heavy burdens; rural counties with a small tax base were forced to the verge of bankruptcy by the increasing costs of providing medical care. Nevertheless, the legislature failed to appropriate any money for Medicaid, even after the program was approved, partly because of concerns about the financial difficulties that other states had experienced with this program.[1]

Arizona thus seemed an ideal setting in which to experiment with a model for fundamental reform of Medicare and Medicaid. With an administration in Washington that was favorable to the idea of "competition" as a strategy for cost containment, a federal waiver was granted, permitting the enactment of an experimental Medicaid alternative, beginning in October 1982. The Arizona Health Care Cost Containment System (AHCCCS) was envisioned by some as a pilot program for national health care.[2]

AHCCCS was designed to replace the fee-for-service type of Medicaid reimbursement with prepaid, capitated financing and a gatekeeper mechanism for cost control. Other "procompetition" features[3] that AHCCCS was supposed to embody included free choice of providers and organization of physicians into groups of diverse types, which were to bid competitively to serve a certain number of patients.

Several types of organizations bid for contracts to participate: health maintenance organizations (HMOs), university clinics, county medical centers and independent practice associations (IPAs), the latter springing up specifically for this purpose. Each contracts with specialists and gatekeepers. The gatekeeper physician is responsible for providing primary care and for arranging specialized services. The incentive for reducing utilization of (that is, restricting access to) expensive, specialized procedures is the prospect (so far illusory) of sharing a "pool" of unused funds at the end of the year.

While it is similar to other prepaid plans in the above respects, AHCCCS also has some distinctive features: all funding is governmental; administration is now directly by government though an intermediary was initially involved; the profit motive has been explicitly introduced into health care for *indigents*; the physician has been assigned the status of a subcontractor (rather than an employee or a contractor).

As the program evolved, its operation diverged from the initial proposal in several ways. First, the hope that once it was set up to care for the needy, the plan would attract others, such as state employees, has not been realized. (This innovative idea of bringing nonindigents into the indigent health care system, the reverse of "mainstreaming" indigents into the private system, was suggested as a quality control mechanism,[2] as well as a means of spreading financial risk over a broader base.) Second, the promised freedom of choice has been sacrificed to a large extent. Third, the method of financing, though presented as capitation, does not actually work in quite that manner. Capitation is the means used by AHCCCS to pay the groups (the "contractors") on the basis of enrollment. However, the individual physicians, pharmacists and others (the "subcontractors") who provide services to patients may be paid on a "capped" fee-for-service basis. While specialists continue to receive a fee for service, the largest IPA started paying the gatekeepers by capitation in October 1984, after filing for reorganization due to bankruptcy.

Although called an experiment, AHCCCS unfortunately was not designed to collect the pertinent data. Interpretations must therefore be made cautiously. On the other hand, the results might be more realistic than those of a more rigorously

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ABBREVIATIONS USED IN TEXT

AAAHC = Accreditation Association for Ambulatory Health Care
AHCCCS = Arizona Health Care Cost Containment System
HMO = health maintenance organization
IPA = independent practice association

controlled experiment, which might not work as well as expected when transferred to the real clinical environment.

In its establishment, AHCCCS has confronted severe difficulties. The name of the program, as well as its pronunciation ("ACCESS"), has become an irony that should be instructive to health planners throughout the nation.

The "Cost Containment" Mechanism

Providers (and Patients) "at Risk"

The gatekeeper is envisioned as the key to "cost containment." The skills described as necessary for the gatekeeper[4] resemble those of a good primary care physician. However, the patient's welfare is no longer his or her preeminent concern. The gatekeeper's incentive to provide "cost effective" treatment is to maximize reimbursement. To prevent "overutilization," the gatekeeper must be placed "at risk," thereby placing patients at risk also, even if unintentionally.

The gatekeeper is subjected to two types of risk: the cost of illness in his or her own patients as well as the costs incurred by the plan as a whole, and increased legal liability.

For the eventuality of catastrophic illness, some type of reinsurance must be provided in a prepaid plan. This mechanism is somewhat vaguely defined in AHCCCS. One IPA set up a "Dr Blackcloud" fund for patients suffering trauma, cancer, renal failure or another condition requiring more than $2,000 worth of services in a year. The gatekeeper managing such a patient was reimbursed on a fee-for-service basis for providing or arranging all needed care. While attempting to assure that gatekeepers would not be penalized for undertaking the care of the sickest patients, this mechanism bypassed the primary cost-control feature of the system. In two studies,[5,6] the 10% to 20% of patients classified as "high cost" generated about half the hospital charges, suggesting that cost-control measures directed only at the healthier part of the population may not have sufficient impact. In any event, the "Dr Blackcloud" method became defunct when that IPA entered bankruptcy proceedings.

For patients who are sicker than average, but not quite sick enough to qualify for the reinsurance, the gatekeeper is at personal risk, originally for a reduction in "bonus" payment from funds in a pool, but now for uncompensated work and for funds directly from the gatekeeper's pocket. The monthly capitation payment is supposed to include hospital care by the primary physician as well as most routine blood tests and radiographs (chest films and many orthopedic films).

The potential financial and legal jeopardy of the gatekeepers is best elucidated by the waiver they must sign in order to participate in one IPA: "The Subcontractor agrees to hold harmless the State . . ., the Administrator . . . and all AHCCCS members in the event of nonpayment by the Contractor to the Subcontractor. The Subcontractor shall further indemnify and hold harmless the State and the Administrator and their agents . . . against all injuries, deaths, losses, damages, claims, suits, liabilities, judgments, costs and expenses . . . which may accrue through negligence or omission of the Subcontractor." Thus, like subcontractors in other industries, gatekeepers must take the risk of nonpayment, even of the agreed-upon-price, while renouncing the legal recourse available to plumbing and electrical subcontractors. The practice of withholding a "pool" to be used as incentive reimbursement can also place gatekeepers in a position analogous to that of subcontractors in the construction industry. Often, while the general contractor is drawing interest on money in the bank, the subcontractors have barely sufficient cash flow to meet their payrolls. (This situation occasioned a recent construction strike in Arizona). Furthermore, the legal implications of deriving profits from the denial of procedures or referrals have not yet been explored in court. By the "hold harmless" clause, the gatekeepers have accepted the liability.

Although the practice of putting physicians at risk is gaining greater acceptance, it should be noted that physicians are different from insurance companies in several ways. An insurance company theoretically risks the investors' capital, but seldom forfeits its assets because of its ability to raise premiums to compensate for losses. While investors have limited control over conditions in the marketplace, they do have the freedom to sell their holdings and cut their losses. In contrast, the gatekeeper is not risking venture capital, but payment for his or her labor. Under terms of the contract, the gatekeeper cannot increase fees to cover extraordinary costs. He or she has little control over many patients' illnesses and has an ethical obligation not to withdraw from a case due to nonpayment. Furthermore, insurance companies spread their risks over a broad base. Although the small number of patients on the panel of some gatekeepers has been recognized as a problem,[4] increasing the number of patients militates against the provision of personal attention to individual patients.

Cost Shifting

Another method used for "cost containment" is cost shifting, both to the private sector and to the non-AHCCCS part of the public budget. Much of the legal and administrative burden has been placed upon private gatekeepers, who—unlike employees of public institutions or most HMOs—must purchase their own liability insurance and provide their own office staffs. The procedures, such as telephone calls to check eligibility and to obtain authorizations for various special services, fill a thick notebook—bound in loose-leaf fashion, to accommodate the frequent changes. Mistakes, particularly failure to verify that a patient's enrollment is current, are punished by nonpayment. Private gatekeepers have said to me that meeting AHCCCS requirements takes from one to four hours of employee time per day. Additional time spent by staff and physicians at evening meetings to keep abreast of administrative developments is, of course, uncompensated. For home care, gatekeepers are urged to take advantage of charitable organizations, in the expectation that such agencies can and will continue to provide, free of charge, equipment and services that patients should be eligible to receive at state expense.

One large administrative cost that is borne by the counties alone is the determination of eligibility. The second largest county (Pima) spent $256,000 for this purpose the year before the program was enacted and $808,000 the year after, due to more stringent requirements and the need for recertification of all enrollees every six months.[1]

TABLE 1.—*Expenditures for Indigent Health Care Before and After AHCCCS**

Fiscal Year	Cost of Indigent Health Care (in millions of dollars)			
	Excluding Long-term Care			
	AHCCCS Eligible	AHCCCS Plus County Eligible	Long-term Care	Total
1980-1981 (pre-AHCCCS)	. . .	92.6	38.2	130.9
1983-1984	216.3	264.7	48.1	317.1†

AHCCCS = Arizona Health Care Cost Containment System

*From Romano.[7]
†Includes $4 3 million in eligibility determinations, which is considered a non-AHCCCS cost.

The most obvious method of cost-shifting is to deny or delay reimbursement to providers. Sixteen hospitals and an ambulance company filed suits because of $8.5 million in allegedly unpaid bills; an additional $24 million is claimed by 5,400 physicians, pharmacists and other providers. The state has disclaimed liability. The lawsuit was dismissed from a Maricopa County court because administrative remedies had not been exhausted (*Arizona Republic,* February 5, 1985, p A2).

Another method of shifting hospital costs to the county (which might, in turn, try to shift it to private hospitals) is through change in the eligibility process for expedited cases (nonenrolled but eligible patients who are admitted to hospitals in emergency situations). Initially, 30 days were allowed to complete the process, with AHCCCS assuming responsibility for the bills retroactively. Recently the time covered by the retroactive payment was decreased to five, then to one day. In December 1984 the expedited application process, which permitted the use of telephone interviews and the acceptance of patient statements if documentation was unavailable, was eliminated altogether (Fran Monachino, former Pima County Eligibility Administrator, oral communication, January 30, 1985). Now it is even more difficult, often impossible, to complete the application in a single day. Thus, the county may be responsible for the initial days of a hospital stay, usually the most costly ones (William Cole, Operations Research Analyst, Pima County Office of Budget and Research, oral communication, January 30, 1985).

Cost Enhancement

Despite its name, AHCCCS has several mechanisms for increasing costs. Most important, a new layer of administration has been added to the existing county bureaucracy. Initially, a private firm was to administer the program: MSGI, owned by McDonnell Douglas. After about a year and a half, the company had accrued huge cost overruns and abandoned the program. Its administrative cost was projected to be about $35 million over the three years of the contract, rather than the $8.2 million bid (*Arizona Republic,* July 4, 1984, p B1). A $450,000 audit, done by a private firm for the state Auditor General, concluded that the program had been set up too quickly and administered badly, but did not take a stand on just how much was owed by the state to MSGI (or vice versa). MSGI sued the state for $17.1 million for the one and a half years that it served as administrator; $11.3 million has been paid to date (*Arizona Daily Star,* February 7, 1985, p A1). The state assumed administration of the program when MSGI abandoned it. Later, the state countersued MSGI for $18.6 million, then amended the complaint to ask for $28 million (*Arizona Republic,* January 21, 1986, p A5). As of early May 1986, the lawsuit remains unsettled.

Another potential source of loss is through graft and corruption. Though various allegations remain unproved, the large accumulation of loosely managed funds certainly provides great temptation and opportunity. One provider group allegedly used for patient care only half of the $8 million they had received, according to an audit by MSGI (*Arizona Republic,* March 22, 1984, p A1). A state grand jury was called to conduct a criminal investigation of the largest provider group (*Arizona Republic,* February 22, 1985, p A1).

In addition to the legitimate and potentially illegitimate overhead, the patient care mechanism is itself inefficient. Patients are required to change gatekeepers every time their provider group loses a bid. About 21,000 patients were forced to dissolve doctor-patient relationships at the county facility, Maricopa Medical Center, when the county's bid was rejected by AHCCCS, causing great emotional distress as well as logistic difficulties and loss of continuity of care. Statewide, about 35,000 patients changed gatekeepers on a single day (*Arizona Republic,* October 3, 1983, p B1). In the second year's bidding the county was awarded a new contract and many patients returned.

Expenditures for Indigent Health Care

Have the cost-saving incentives outweighed the factors that increase costs? In theory, this should happen only if the indigent patient population had been receiving excessive services in the past, a situation for which no evidence has been presented and which would be surprising. Even before AHCCCS, the county hospitals were structurally like closed-panel HMOs, the arrangement that is reputed to be the most cost-effective one. In practice, the expenditures for indigent health care have increased substantially, as shown in Table 1. While the expenditures for long-term care, which remains the responsibility of the counties, increased 26% over a three-year period, other expenditures (excluding eligibility) increased by 186%.

Nevertheless, a report to the state legislature[7] claims that AHCCCS saved $11 million over the projected cost of health care for indigents in fiscal year 1983-1984.

It is true that health care costs in Arizona have risen rapidly. The medical cost component of the Phoenix Metropolitan Consumer Price Index in 1981-1982 was 12.1%, in 1982-1983 it was 14.3% and in 1983-1984 it was 10.3%. Using this inflation rate, the cost of caring for an indigent person might have been expected to rise from $766 in 1980-1981 to $1,082 in 1983-1984. The projection used in the legislative report assumes an increase to $1,367 per person,[7] an increase of 78% over the three years instead of the 41% expected from the observed inflation rate.

In its projection, the state also assumes a large increase in

the number of indigents, which seems unlikely since state expenditures for welfare increased by only 10.6% between fiscal years 1980-1981 and 1981-1982 and by an estimated 2% between 1981-1982 and 1982-1983.[8] According to the Health Systems Agency of Southeastern Arizona, which is responsible for health planning, to obtain reliable statistics on the number of indigents would require establishing a consistent definition and method of counting, neither of which have been used. Because the counties had a negative incentive to do case finding, whereas providers paid by capitation have a positive incentive, it is difficult to interpret the statistics. In 1980-1981 the number of eligibles served by the counties was 120,992 and in 1983-1984 the number served by AHCCCS was claimed to be about 169,000.[7] However, an accurate number of AHCCCS-enrolled patients who have actually utilized services is not known.

Although initially motivated by a wish to aid the overburdened counties, the enactment of AHCCCS has been accompanied by a substantial increase in the counties' expenditures for indigent care. Total county costs, as reported to the state Auditor General,[7] were $130,879,226 in 1980-1981. In 1983-1984 the counties contributed $63,073,476 to the AHCCCS budget, and in addition spent $4,353,687 on eligibility determinations, $48,407,407 on the care of the "notch group" (persons eligible for county assistance but not meeting the more stringent AHCCCS criteria) and $48,049,191 on long-term care—a total of $163,883,761, a 24% increase over three years. This increase in actual expenditures is strikingly close to the increase that might have been expected without AHCCCS, according to a projection by the Pima County Office of Budget and Research (William Cole, Operations Research Analyst, Pima County Office of Budget and Research, written communieation, December 1984). The infusion of $82,371,000 from the state, $53,679,400 from the federal government and $17,231,800 from unstated other sources in 1983-1984[7] did not buy much relief, although some of the burden has been shifted from the smaller to the larger counties. Furthermore, the amount of free care contributed (voluntarily or not) by hospitals, physicians and other providers is unknown and probably undeterminable.

Part of the cost overrun has been attributed to the "fee-for-service window," the period of time between enrollment in the program and selection of a gatekeeper. It would seem that if some patients undertake the lengthy enrollment process only if, when, and because they happen to be sick, initial costs might be higher than average regardless of the reimbursement method. In any case, this "window" was closed early in 1984, at least for the medically indigent/medically needy category of patients, who are now automatically assigned to a provider upon enrollment (as discussed later).

Access

It is not clear that the program has improved access to care; in fact, the contrary may be the case for many patients, especially for those who fail to meet the eligibility requirements, which are exceedingly restrictive. A family of four with a total annual income exceeding $4,183 is ineligible.[9] Requirements have been tightened so that income for a 90-day rather than a 30-day period is used to determine eligibility.[10] Many patients have complained about the difficult enrollment process[1] (*Arizona Republic,* October 3, 1983, p B1). Indeed, enrollment of medically needy patients has declined from a peak of 80,169 in May 1984 to 63,383 in January 1985, though enrollment of categorically eligible patients increased from 109,072 to 115,886 over the same period (according to official AHCCCS figures).

Initially, patients were allowed 30 to 45 days after enrollment to choose a provider. Although categorically eligible patients (such as those receiving Social Security disability or Aid to Dependent Children) still have 30 days to choose their gatekeeper, as required by the federal waiver, freedom of choice for the medically indigent or medically needy has been sacrificed to the budget. Because of assignment on the basis of postal ZIP code, some patients who live five miles from the rural Marana Clinic must go to Casa Grande, 40 miles away.[11]

The only study comparing health care for the poor in Arizona before and after the implementation of AHCCCS was carried out by the Flinn Foundation in 1982 and 1984.[12] Persons eligible for AHCCCS did report gains in access to health care. The percentage stating that they lacked a usual source of medical care declined from 15.3% to 5.2%. However, among all the poor, the percentage claiming lack of a usual source of care increased from 15% to 18%, with all the increase occurring among those ineligible for AHCCCS (the "notch" group). Fully 15% of AHCCCS ineligibles said that they found it more difficult to obtain health care in 1984 than they had before the AHCCCS program began. About 16% of AHCCCS-eligible patients also found it more difficult to obtain care under the new program, while about 25% of AHCCCS eligibles found it less difficult.

Quality

Reimbursement by capitation could financially punish conscientious physicians for providing good care to their patients (a problem inherent in any fixed sum system), while rewarding "entrepreneurs," who plan to profit by enrolling patients and then minimizing the financial losses involved in caring for them. Expensive advertising campaigns—television and radio announcements, billboards[13] and newspaper displays—suggest that profits were indeed anticipated.

Therefore, a quality assurance program is essential, but two of the three proposed mechanisms[2] have not been effected. The inclusion of indigents has not occurred. Patient mobility is at best an awkward means (even with an adequate computer system) and has now been largely eliminated by state assignment of providers. A third mechanism, periodic monitoring programs, has recently been implemented in the form of limited audits of facilities and patient records.[14]

Evidence for denial of services is anecdotal but disturbing. An investigative reporter for *The Arizona Republic*, a Phoenix newspaper, obtained recordings of conversations among owners of one IPA, who discussed the need to gain more control over referrals and hospitals in order to diminish costs. In one case, two ophthalmologists attempted to interfere with surgery on a patient who had suffered hand trauma (*Arizona Republic*, December 26, 1983, p A1). While such reports do not constitute scientific evidence, they should not be ignored, especially given the paucity of data to show that patients *do* have access to needed services.

Patient Satisfaction and Process Data

Data about present quality of care are scanty. Two surveys

TABLE 2.—*Deliveries in Arizona Without Adequate Prenatal Care*

Year	(Rate per 1,000 Births) 1979	1980	1981	1982	1983
Births with fewer than five prenatal visits . . .	92.4	84.9	76.9	75.9	79.0
Births with no prenatal visits	18.0	20.0	19.5	18.9*	21.3*

AHCCCS began in October 1982

*Difference significant, *P* less than .01

in the Phoenix area reported that about 75% of the enrollees were satisfied with AHCCCS[10]: one IPA sponsored interviews of 278 patients and an independent research firm surveyed an unspecified number. Satisfaction, of course, is not the same as quality.

An MSGI audit of 15 provider groups reported that, overall, care seemed equivalent to that received by non-AHCCCS patients seeing the same physicians on a private basis (*Arizona Republic*, December 26, 1983, p A1). The medical director of MSGI resigned, however, after charging that the program was providing poor care (*Arizona Republic*, November 13, 1983, p C1).

The most extensive study available is an audit conducted by the Accreditation Association for Ambulatory Health Care (AAAHC).[15] The study does not claim to be scientifically valid, since the individual providers within the 19 plans were selected by AHCCCS staff, using criteria unknown to the AAAHC. The providers were notified in advance of the time and place of the audit. About 1,223 records were reviewed at 63 sites. The primary focus of the audit was to assess compliance with selected standards in the 1982-1983 edition of the *Accreditation Handbook for Ambulatory Health Care* (Accreditation Association for Ambulatory Health Care, Inc, Skokie, Ill, 1982). Overall, the auditors concluded that 4% of the records were illegible; 30% did not have an adequate history and physical, considering the chief complaint; 12% did not have an appropriate diagnosis or assessment; 9% had inadequate treatment; 39% did not have the patient's allergies noted in the record. Apparently, the physicians performing the audit felt capable of reaching a judgment about the clinician's diagnosis and treatment, even in those instances in which the history and physical were considered insufficient. The quality of care at each location was assigned a rating: "very poor," "fragmentary," "unable to be determined due to scarcity of information in the record," "average," "above average," "appropriate," "adequate," "good" and "very good." The terms are not defined. Some serious problems were identified: failure to refer a patient with a breast mass and one with rectal bleeding; no regular prothrombin times in an anticoagulated patient with two prosthetic heart valves; treatment of a child with congenital heart disease for a dental abscess without antibiotics; no follow-up on two cases of otitis media with perforations; delay in referral for colon carcinoma; failure to follow up a patient with positive serology for syphilis; diagnosing abdominal pain as "anxiety" without performing any evaluation at all, and several less serious omissions.

The report concluded that the AHCCCS providers rendered similar care to their AHCCCS and their private patients, though no pertinent data were cited. Despite the shortcomings of the study, its authors believe it to be the most thorough review of any Medicaid program in the United States.[15]

Outcome: Preliminary Prenatal Care Statistics

One of the more sensitive barometers of access to care is prenatal care. The rate of births with no or with fewer than five prenatal visits is given in Table 2. Preliminary statistics for 1983 show a reversal of the previous downward trend; in 1983, the number of births with no prenatal care at all was up 12.7% compared with 1982 ($P < .01$). The increase seemed to begin about September.[16] AHCCCS was begun in October 1982. Because of the preliminary nature of the data, it would be premature to draw definite conclusions about the impact of AHCCCS.

Effect on County Hospitals

The county hospitals experienced adverse effects during the implementation of AHCCCS. Maricopa Medical Center in Phoenix had to close two primary health care centers and to cut back on services in rehabilitation, respiratory care, patient education and home health care due to lack of funds. Up to 60% of personnel on some floors were registry nurses, unfamiliar with the system and hired at higher cost because of attrition among the regular staff. Due to uncertainty about the fate of the hospital, fewer highly qualified candidates applied for house staff positions at a center that is known for some of the best residency programs in the Southwest.[17] Some of these problems seem to have been temporary, the result of an adjustment period and loss of an AHCCCS contract that has been restored (at least for the present). The fate of the county hospital in the second largest county, Pima, remains undetermined. That hospital will no longer be able to fund a medical residency.

Should AHCCCS Be Continued?

Despite its serious problems, AHCCCS has many defenders, who attribute its difficulties to a few unscrupulous or incompetent persons, an inadequate computer system, insufficient experience with prepaid programs or too rapid implementation. Many are determined to overcome these "growing pains" and to "make the system work."[1,10,18] Recent changes, including the appointment of a new medical director, have given rise to some optimism. Nevertheless, incidental problems should not be allowed to divert attention from an evaluation of inherent flaws in structure and incentive.

Is the gatekeeper concept sound? So far, AHCCCS has not contradicted evidence from the United Healthcare Corporation IPA that primary care coordination by a gatekeeper is not sufficient to contain health care costs.[19] Arguably, the full effect of the capitation incentive has not yet been felt—either on costs or on quality. Do gatekeepers neglect to order indicated films when they receive the bill for this service themselves? If so, it should be noted that AHCCCS would not save any money at all (since it has already paid the capitation). Will primary physicians provide "capitated" services themselves—at no extra pay—when they can? Or will they refer the patients to specialists, who are paid from a pool rather than from the individual gatekeeper's pocket? If so, costs will increase. In the United Healthcare Corporation experience, expenditures for referral care actually did rise.[20] Examinations of the AHCCCS system to date have not addressed these

questions, which will be difficult to answer, especially since they might require self-incrimination by physicians. Similar concerns about the perverse incentives of capitation have been raised in California, where sweeping changes are being made in the Medi-Cal program.[20]

Physicians and medical educators[18] have found the gatekeeper concept appealing, possibly as a way of regaining status that the primary care physician has lost to the subspecialists. However, this hopeful outlook disregards the implications of being a subcontractor when the contractors demand cost containment and delegate the responsibility for denying requests for care. The reality is not changed by using the term "managing" rather than "rationing." Though the primary physician has traditionally been the patient's advocate, the gatekeeper is potentially the adversary, both of the patient and specialist colleagues.

Does prepayment make medical care more economical? While "cost containment" is generally understood to mean "forcing providers to be more efficient," in actuality it can translate into reducing services or shifting costs. In AHCCCS there is no evidence that the cost per service has diminished; in fact, the unit cost cannot be calculated due to lack of information about the number of services rendered.[10] Even federal officials have had difficulty obtaining information about the patient utilization of health care facilities (*Arizona Republic*, May 10, 1984, p B1). But unquestionably, total *expenditures*, as distinguished from unit costs, have increased greatly, even without including the as-yet-unknown costs of pending litigation.

Has the use of private providers improved access to care? For eligible patients, there are obstacles to enrollment and the need for frequent recertification. For patients who are a little better off, there is the tendency to tighten the eligibility requirements when the budget is strained. The availability of care to poor but ineligible patients might be lessened further if the counties divest themselves of their hospitals, as the Pima County Board of Supervisors has contemplated. The county hospital in the past accumulated many bad debts because of a policy of treating emergencies first, and worrying about eligibility later (William Cole, Operations Research Analyst, Pima County Office of Budget and Research, oral communication, December 31, 1981).

Have standards of care been maintained? There are several reasons for concern. One is that the design of the system tends to reward profit-seekers and to burden the conscientious physician. Second are the increasingly complex and time-consuming administrative strictures which potentially could interfere with providing care. Finally, loss of continuity of care is built in. Some evidence suggests that, just as expected, patients do fare better when they are seen by the same provider repeatedly.[21] However, despite acknowledging the need for monitoring, AHCCCS has done little to implement a consistent mechanism for "quality assurance."

At present the high cost of AHCCCS, combined with the undetermined quality of care and the possibly diminished access to care, would appear to me to favor dismantling the program and returning to the old county system, perhaps with deficits funded by the state if necessary.

Several obstacles impede a return to the previous system, once an entity like AHCCCS has been established. Great political momentum has been generated by the experiment, as politicians have staked their careers on its survival. Groups of physicians, set up to bid for AHCCCS contracts, derive a substantial portion of their income from it. While at present such groups have a vested interest in its continuation, nothing prevents their withdrawal from indigent care if reimbursement becomes less attractive or if they should manage to attract groups of paying patients, as was their initial ambition (unpublished letter from Directors of Arizona Family Physicians IPA to Arizona physicians, July 26, 1983). It would indeed be ironic if funds intended for indigent care subsidized the start-up of a new private delivery system. Finally, damage to the previous system might become irreparable[22]—for example, if the counties were to sell their hospitals.

Conclusions

The outcome of the Arizona experiment is especially important for primary care physicians as they are recruited for the gatekeeper role, as well as for taxpayers and, above all, for patients.

The results to date appear consistent with expectations based on the incentives inherent in the system. Expenditures have nearly tripled, without any evidence that three times as much care has been provided to the poor. The evaluation is complicated by the fact that, unlike in a scientific experiment, no provision was made in advance to collect the pertinent data for either the experimental or a control group. But the burden of proof rightfully belongs to the innovators, who need to answer many questions before perpetuating the AHCCCS concept, in Arizona or elsewhere.

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The AHCCCS Director Responds

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I agree, as Dr Jane Orient states in her article ("Arizona Health Care Cost Containment System—A Prepayment Model for a National Health Service?"), that the outcome of the AHCCCS demonstration is important for physicians, taxpayers and patients. This was the main reason I became director of AHCCCS in April 1984. At that time AHCCCS faced severe administrative difficulties. Since AHCCCS began operation on October 1, 1982, it had experienced a number of problems, many of which could be traced to a lack of adequate time for planning, the experimental nature of the AHCCCS concept and the lack of available expertise in prepaid medicine.

AHCCCS is the nation's first statewide program to provide medical service on the prepaid concept as opposed to conventional fee-for-service in other Medicaid states. AHCCCS is a demonstration project aimed at testing the use of prepaid, capitated financing of health care services for indigents and other eligible state residents.

Dr Orient raises four interesting questions in her article:

- Should AHCCCS be continued?
- Is the gatekeeper concept sound?
- Does prepayment make medical care more economical?
- Have standards of care been maintained?

These questions are valid and should be addressed. AHCCCS was designed to provide health care and to evaluate these questions. Scholarly research, based upon current, accurate and adequate information, can be exciting and provide an educational opportunity for all interested parties. Such research should communicate facts and further the understanding of AHCCCS.

Unfortunately, Dr Orient's article perpetuates misunderstanding of AHCCCS. If you want a careful, scientific and deliberate analysis of AHCCCS based on fact, her article will be of little value. Dr Orient's questions have merit, and they should have responsible answers.

Is the Gatekeeper Concept Sound?

I would like to take this opportunity to respond to what Dr Orient perceives as the answer to her questions. To provide perspective I will address the question regarding the future of AHCCCS last and the gatekeeper question—"Is the gatekeeper concept sound?"—first. Dr Orient dismisses the gatekeeper as a sound medical concept. Dr Orient's argument against this concept is based on the assumption that all AHCCCS gatekeepers or primary care physicians (PCPs) are capitated and, therefore, they are all at risk. Among AHCCCS health plans, some PCPs are capitated. Capitation is not the only contract form between PCPs and health plans. For instance, the two main county health plans (Maricopa and Pima) and the University of Arizona's health plan are staff models. Two of the largest health plans (Arizona Physicians-IPA and Access Patients Choice, Inc) have modified fee-for-service and capitation agreements. Therefore, the assumption that all AHCCCS PCPs are at risk is incorrect.

Should a health plan fail, a capitated PCP may be at risk. However, AHCCCS has developed a bonding structure to reduce this risk. Health plans are now required to either secure an irrevocable letter of credit, execute a performance bond of standard commercial scope or provide a cash deposit to AHCCCS. In the event of a default by the health plan, AHCCCS will execute on the bond for the purpose of mitigating any damages incurred by providers.

Dr Orient presents an example of the potential financial and legal jeopardy of PCPs. This example is the indemnification and insurance clause from a health plan's subcontract. This clause does place the PCP at financial and legal risks as a result of the PCP's negligence or omission. This clause does limit the responsibility of the state in case the contracting health plan fails to reimburse the PCP subcontractor. In instances of dispute regarding payment for services, the health plan maintains a system for grievances. The health plan is required to provide a responsive system to resolve grievances and this system is available to the PCP. Thus, the PCP has a process for relief should there be a payment dispute.

In citing the evidence from the United Healthcare Corporation (IPA) experience, Dr Orient makes a mistake common to those unfamiliar with the prepaid concept. According to the article referenced by Dr Orient, United Healthcare used a fee-for-service reimbursement system. Furthermore, the referenced article concluded that the adequate incentives were not applied for the PCP to control the use of services. In fact the article references the working of a group account system. This is in no way similar to the AHCCCS model.

Paraphrasing a conclusion in an article in the December 1983 *New England Journal of Medicine (NEJM)* on the SAFECO experience, Dr Orient says, "So far, AHCCCS has not contradicted evidence from the United Healthcare Corporation IPA that primary care coordination by a gatekeeper is

(Schaller DF: The AHCCCS director responds. West J Med 1986 Jul; 145:120-123)

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ABBREVIATIONS USED IN TEXT

AAAHC = Accreditation Association for Ambulatory Health Care
AHCCCS = Arizona Health Care Cost Containment System
PCP = primary care physician

not sufficient to contain health care costs." That's not exactly what the authors of the *NEJM* article concluded, although it is a portion of one of their conclusions.

"In our view, the SAFECO experience shows that primary-care coordination *by itself* [emphasis added] is not sufficient to control health care costs," the authors of the *NEJM* article said. Dr Orient misinterpreted a statement from a referenced article and tried to prove that AHCCCS does not work. I agree with most of the conclusions in the *NEJM* article and would point out that AHCCCS has enacted many of the recommendations cited in the article.

According to Dr Orient

> the patient's welfare is no longer his or her [the gatekeeper's] preeminent concern. The gatekeeper's incentive to provide "cost effective" treatment is to maximize reimbursement. To prevent "overutilization," the gatekeeper must be placed "at risk," thereby placing patients at risk also, even if unintentionally.

Dr Orient's inferences that physician motives are based upon profit rather than ethical health care considerations are offensive to me as a physician and to the medical community. If Dr Orient has any evidence of a physician placing a patient's welfare at risk, either intentionally or unintentionally, she has a duty as a private citizen and public servant to present it to me and the appropriate medical regulatory boards.

Dr Orient presents no evidence to support the claim that PCPs are required to deny needed care and assume an adversarial role with the patient. AHCCCS has a comprehensive utilization review system designed to ensure that AHCCCS members receive the medical care they need.

Does Prepayment Make Medical Care More Economical?

"Does prepayment make medical care more economical?" is an interesting question and one that must be answered. The charge that "cost containment" means reducing services or shifting costs is unsupported. The AHCCCS program has a system to verify a person's eligibility for services and that system is responsive to the PCP. The time and effort required to verify enrollment has been reduced continually. To protect the PCP from uncompensated care, many health plans have prior authorization systems. Should a PCP fail to verify a patient's enrollment or obtain prior authorization, then that PCP may be at some risk.

Furthermore, Dr Orient suggests that, "The most obvious method of cost-shifting is to deny or delay reimbursement to providers." As evidence of "cost shifting," Dr Orient cites a lawsuit filed against the state by hospitals, physicians and others. That suit was filed by providers who had claims against one health plan at the time it filed a bankruptcy petition. That is hardly an example of willful cost shifting. Furthermore, bonding provisions would now protect against this.

The cost shifting examples are insufficient to answer the question posed by Dr Orient. The facts, as presented by Dr Orient, do not support her conclusions.

Has the Use of Private Providers Improved Access?

The access to care question ("Has the use of private providers improved access to care?") is one in which I have professional interest. Dr Orient states that "persons eligible for AHCCCS did report gains in access to health care" but totally ignored this fact in presenting the conclusions.

I must stress that AHCCCS is designed to serve those who are eligible. The important fact is that there is empirical evidence that AHCCCS has improved access to care for those people eligible. Dr Orient's confusion regarding eligibility requirements and access to care is puzzling. Because AHCCCS has eligibility provisions is not justification to dismiss the program.

Dr Orient also contends that about 21,000 patients "were forced to dissolve doctor-patient relationships at the county facility, Maricopa Medical Center, when the county's bid was rejected by AHCCCS. . . ." It is true that the Maricopa Health Plan lost a portion of its contract in 1983 and 15,000, not 21,000, members had to select another health plan during the annual open enrollment process that is available to all AHCCCS members. The remaining 6,000 members who left Maricopa were not forced to switch health plans but did so voluntarily during the open enrollment process.

Dr Orient further contends that 35,000 patients statewide "changed gatekeepers on a single day." That occurred in 1983, during the program's first open enrollment process and at the end of the first year of operation. The reason the figure was high was twofold: (1) The figure included the 15,000 members that Maricopa Health Plan lost and (2) About 20,000 members chose to switch health plans voluntarily. The latter number was high but not surprisingly so considering 1983 was the first year of operation. Moreover, switching health plans is what open enrollment is all about—freedom of choice, which is what Dr Orient claims is missing in this program.

AHCCCS has had two open enrollment periods since the one in 1983. About 14,800 members changed plans in 1984 and 9,994 (or roughly 6% of our total membership) changed plans in 1985.

Have Standards of Care Been Maintained?

In addressing the question concerning standards of care ("Have standards of care been maintained?"), Dr Orient charges that AHCCCS has done little to implement a consistent mechanism for "quality assurance." AHCCCS has a quality assurance program that is designed to ensure that the delivery of cost-effective medical care does not compromise quality. This program is designed to assure that beneficiaries are provided care that equals or exceeds the quality of services provided to the general fee-for-service public. Each health plan is required to have a formal quality assurance review plan that continuously monitors quality of care.

The AHCCCS Medical Director, Albert W. Bostrom, MD, reviews the adequacy of the design and implementation of the quality assurance review plans. He works with each health plan's medical director to ensure that the quality assurance review plan is professional and functional.

AHCCCS actively monitors this critical component. Each year the AHCCCS program conducts an independent medical audit of the health plans. The audit that Dr Orient referred to

in her article was conducted by the Accreditation Association for Ambulatory Health Care (AAAHC) under contract to AHCCCS. Of the audit, AAAHC said, "It remains, to our knowledge, the most thorough review of any Medicaid program in the United States." Dr Orient failed to note the actions taken by AHCCCS as a result of the audit. AHCCCS assisted each health plan in addressing identified problems. There was considerable follow-up in every case.

Dr Orient states that preliminary statistics for 1983 show the number of births with no prenatal care had increased 12.7% compared with 1982. She then states, "Because of the preliminary nature of the data, it would be premature to draw definite conclusions about the impact of AHCCCS." If that is true, why mention it? If the author had been informed on this issue, she would know that other areas of the country are experiencing similar problems. The problems are not unique to Arizona and they are not just medical, but financial, social and cultural. Futhermore, the statistics are presented by Dr Orient without the explanation that they cover the state's entire population, including insured and self-pay people.

Should AHCCCS Be Continued?

Now to the final question: "Should AHCCCS be continued?" Dr Orient stated that "At present the high cost of AHCCCS, combined with the undetermined quality of care and possibly diminished access to care, would appear to me to favor dismantling the program and returning to the old county system, perhaps with deficits funded by the state if necessary." This statement is both contradictory and confusing.

To those unfamiliar with the history of indigent health care in Arizona, it would appear that Dr Orient makes a valid case regarding expenditures for indigent healthcare. The counties had been responsible for indigent health care in Arizona since before statehood in 1912. In 1974 the Arizona Legislature passed a bill authorizing the state to join the federal Medicaid program. However, the legislature did not appropriate any funds and the counties remained responsible for indigent health care. In 1981 the legislature responded to growing fiscal concerns from the counties and created AHCCCS.

Differences between the county system and AHCCCS are pronounced. There were separate and distinct eligibility requirements and processes for each county. Levels of services varied by county; what was a covered service in one county was disallowed in another. This system of health care for indigents was confusing and forced many indigents to accept a lower standard of health care.

AHCCCS has uniform standards for state-supported indigent care and a minimum health care service package. AHCCCS standardized the eligibility requirements and process.

AHCCCS replaces traditional Medicaid fee-for-service with a prepaid health care delivery network. AHCCCS provides quality mainstream health care to eligible people, contains costs and provides a stabilized annual base from which the state, county and federal governments can predict the amount of funding that will be necessary for the required services.

Dr Orient attempts to discount AHCCCS because of an alleged increase in the counties' expenditures for indigent care. Dr Orient, to prove the increase in cost, compares the cost of the ad hoc county system with the cost of AHCCCS with no attempt to adjust for differences between the programs. This process lacks the rigors of quantification and produces misleading results.

Dr Orient may disagree with the AHCCCS concept but she has a professional responsibility not to allow personal objectives and values to bias the analysis. The use of undocumented personal communication is an example of an inadequate understanding of the accepted research methods.

Analyzing the cost of AHCCCS is difficult. It is impossible, given space limitations to present the data necessary for such an analysis. The Health Care Financing Administration has entered into a contract with the Stanford Research Institute for this analysis.

Dr Orient's position regarding the alleged increase in cost is untenable. The evidence to support her claim is misleading. There was no analysis of how the $63 million the counties contribute to AHCCCS was computed. By state law, the counties contribute to AHCCCS one half of what was budgeted or spent on indigent care in 1980-1981, whichever was less. This amount was adjusted to compensate for service provision differences between the county-based program and AHCCCS. The $63 million amount is stable. Counties are not required to contribute any other amounts, even though enrollment may increase. The number of people served by AHCCCS is substantially greater than the number served under the "old" county system. It is unfortunate that Dr Orient attempted to ignore this fact.

It may be inviting to include the amounts from the state and federal governments, but it is improper. The state is capitated by the federal government for those people who receive Aid to Families with Dependent Children or Supplemental Security Income benefits. The health care costs for the state-eligible group—Medically Indigent/Medically Needy (MI/MN)—are borne by the state. These are in effect new dollars and are intended to be used to serve groups of people, some of whom may not have been served by the old county system in 1980-1981. The mixing of "notch group" cost with AHCCCS cost is misleading. The question of providing services to the "notch group" is serious. However, AHCCCS was intended to provide health care to those who are eligible. This is why the county contribution is set at one half of the counties' 1980-1981 health care budget or actual expenditures.

The addition of the counties' cost for long-term care to the AHCCCS cost is improper. These are "room and board" costs and by state law are the responsibility of the counties. AHCCCS has contracts to provide for the medical costs of those eligible persons residing in long-term care facilities.

Like a child in a candy store, Dr Orient went through a legislative report prepared by Marie Romano, selectively quoting figures that tended to support Dr Orient's contentions on AHCCCS costs versus costs under the old county health care delivery system. While Dr Orient correctly quoted an $11 million savings cited by the report, she ignored a number of other statistics presented in the report that would not support her conclusions.

As an example, the $11 million savings was the difference between what it would cost the counties if they provided AHCCCS covered services to AHCCCS eligible people ($328,230,294), minus what was spent on all indigent health care statewide in fiscal 1983-1984 ($317,165,961). However, according to the report, for the counties to provide those

services to those people, the counties would have to increase their budgets by $164,346,533.

The report contains other costs comparisons for fiscal 1983-1984 and fiscal 1984-1985, based on service and eligibility levels. Those figures indicate even greater savings to the counties.

Dr Orient is fully prepared to dismiss AHCCCS based on quality of care and access to care issues. However, in both cases Dr Orient is categorically mistaken. AHCCCS does have an excellent program to evaluate quality of care and a corrective action plan to educate PCPs when substandard patterns are found.

Dr Orient submits that AHCCCS has improved access to care for those eligible. It may be comfortable to blame AHCCCS for access to care problems of the "notch group," but it is incorrect. AHCCCS is responsible to provide care to those people who are eligible—and AHCCCS has fulfilled this responsibility. I agree that providing health services to the notch group is important, but to dismiss AHCCCS on this issue is unfounded and inappropriate.

In summary, it is evident that Dr Orient has failed to provide current, accurate and adequate information concerning AHCCCS. I respect and applaud scholarly research based on empirical evidence. When scholarly research is pushed aside for value judgments, then the entire medical profession suffers.

Alternative Birth Practices and Settings—Indications of Prevalence and Use Among California Obstetricians

ROGER J. PURDY, *San Francisco;* ALAN L. LASNOVER, MD, *Cupertino, California, and* W. BENSON HARER, Jr, MD, *San Bernardino, California*

Interest among women and families in "alternative" birth practices and settings has grown steadily in recent years, but little information has been available about the response of the medical profession to the desire for a more "natural," self-directed and family-centered childbirth experience. Data from a recent survey of California obstetricians, however, indicate that although home birth and delivery in freestanding alternative birth centers are discouraged or not permitted by most respondents, a large majority encourage and/or permit routinely or on request a wide variety of practices that represent departures from previous norms of clinical practice. Results of this study suggest that as long as the safety of the mother and infant are not jeopardized and unacceptable liability risks are not posed, physicians are increasingly willing to accommodate the preferences of patients and families for a more "high-touch" approach to counterbalance the increasing utilization of high technology in obstetrics.

(Purdy RJ, Lasnover AL, Harer WB Jr: Alternative birth practices and settings—Indications of prevalence and use among California obstetricians. West J Med 1986 Jul; 145:124-127)

Interest in alternatives to traditional birth practices and settings has increased steadily among health care consumers in recent years. As hundreds of reports in the professional literature testify to the increasing utilization of high technology in obstetrics, a similarly sizable body of articles in lay publications shows a concurrent and perhaps correlative growth in sentiment for a more "high-touch" approach to the childbirth process. Women in particular have expressed interest in a more "natural" birth experience that is self-directed and family centered, and increasingly advocate birth practices and settings that may include the presence of family members, delivery in alternative birth centers and early parent-infant interaction. Proponents of such practices claim the existence of a wide variety of physical, psychological and social advantages in these alternative approaches.

Although interest in more natural and couple-caring obstetrical support is apparent among consumers, little is known about the response of the medical profession to the rise in consumer demand for alternative approaches to obstetrical care. To gain an indication of the prevalence and use of alternative birth practices and settings in California, data from an obstetric practices survey conducted by the California district of the American College of Obstetricians and Gynecologists (CAL-ACOG) were examined to determine the extent to which alternative procedures and settings are being encouraged or utilized by obstetricians in the state.

Methods

To elicit information about current practices of obstetricians in California, CAL-ACOG's Committee on Obstetrical Practice developed a three-page mail survey instrument listing 61 obstetrical procedures or practices with corresponding fixed response alternatives pertaining to the prevalence of each with physicians' own medical practices. Listed items were grouped under the general categories of management of routine labor, management of routine birth, cesarean birth practices, alternative birth practices and prenatal and postpartum care. A study by Dobbs and Shy,[1] which examined practices associated with alternative birth rooms in Washington State hospitals, was used to select items representing alternative birth practices.

In October 1983 the questionnaire was mailed to 1,185

Drs Lasnover and Harer were members of the Obstetrical Practice Committee of the American College of Obstetricians and Gynecologists, District IX, which sponsored the study reported herein. Mr Purdy is Manager, Department of Research, Division of Research and Socioeconomics, California Medical Association.

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physicians selected randomly from among the 1,806 California Medical Association (CMA) members whose primary specialty was listed in CMA records as obstetrics or obstetrics-gynecology. Following a second mailing to nonrespondents approximately a month later, a total of 502 usable responses were received. Ninety-two questionnaires were returned unanswered by physicians who indicated that they no longer practiced obstetrics or had been identified erroneously as obstetricians in the sample selection; excluding these physicians, the pool of potential respondents was reduced to no more than 1,093 and the net rate of response was 46%.

Analysis revealed the responding sample to be representative of the geographic distribution of California obstetricians but weighted slightly toward physicians in older age groups. Women, who represented an estimated 13% of California's practicing obstetricians and 9% of those who were CMA members in 1983, made up only 6% of the respondent base. Data that would permit an assessment of the representativeness of the sample in terms of other sociodemographic characteristics were not available.

With reference to the management of routine labor, respondents were asked to indicate the frequency with which they order various medical procedures and the degree to which they encourage or permit practices such as ambulation in labor and the presence of the father or other support persons. To measure the prevalence of other obstetrical procedures and practices, respondents were asked to select one of the following alternatives that best described their current practice: encouraged, permitted or performed routinely, permitted or performed on request, discouraged or not permitted or performed. Consistent with the objectives of the study, the marginals or raw frequencies were computed.

For purposes of the present investigation, data from the CAL-ACOG survey were manipulated to combine the percentage of respondents who indicated that they encourage a practice or procedure with the percentage who said they permit or perform it routinely. Percentages in the "discourage" and "do not permit or perform" categories were similarly combined. Although these paired descriptors do not necessarily coincide (a practice might be "encouraged" without being performed *routinely*, for example, or might be "discouraged" but still permitted on request), this methodology was followed in an attempt to impart coherence to the set of response alternatives, which pertained to both *permissiveness* and *endorsement* of practices. Tabulated in this manner, the results provide a general indication of the degree to which various obstetrical practices and procedures are accepted or allowed by California obstetricans.

Results

Information provided by respondents about the frequency with which they order various procedures associated with the management of routine labor suggests that several once-standard practices are no longer employed routinely by most obstetricians. As seen in Table 1, the complete perineal shave appears to have been replaced almost entirely by the mini-prep or no prep at all. More than two fifths of respondents (43%), in fact, order even a partial or mini-shave only rarely or on specific indication, if at all. Fewer than half of respondents order enemas or hypodermic analgesics on a routine or usual basis, and only 8.2% indicated routine or usual use of epidural or caudal anesthesia. A further indication of changing practice patterns is seen in the large proportion of respondents—more than nine in ten—who encourage or permit ambulation in labor, labor in the patient's most comfortable position and the presence of the father or other support persons throughout labor.

While large percentages of respondents indicated that they encourage or routinely perform deliveries in conventional delivery rooms (84%) and in the traditional lithotomy position (80%) and continue to perform episiotomies (76% in primigravidas, 48% in parous parturients), most appear to encourage, routinely permit or be amenable to patients' preferences with respect to a variety of nontraditional practices. Among various practices listed on the questionnaire that reflect a more "high-touch," family-centered approach or represent departures from previous norms of clinical practice, the only practices that are discouraged or not permitted by more than half of respondents are the presence of siblings at birth, the assistance of the father in delivery of the infant and delivery in freestanding alternative birth centers or at home (Table 2). Although some practices are encouraged or permitted routinely by relatively few respondents, they nevertheless appear to be available options for patients—permitted on request—in most cases. For example, delivery without stirrups and discharge within 6 to 12 hours of birth are practices few respondents encourage or permit routinely, but with respect to which most are willing to accede to patient preferences. Similarly, delivery in a hospital-based alternative birth area and dimmed lighting in the delivery room are encouraged or permitted routinely by only one in four respondents but permitted on request by nearly half.

Age-related differences were observed in the pattern of response to many items on the questionnaire and would appear to strengthen the indication of shifting norms in obstetrical practice suggested by the aggregate data. Comparing the percentages of respondents in different age groups who en-

TABLE 1.—*Prevalence of Selected Procedures and Practices Associated With Management of Routine Labor* (N = 502)*

Procedure	*Ordered Routinely or Usually (With Rare Exception) (%)*	*Ordered on Indication or Request Only (%)*	*Rarely or Never Ordered (%)*
Complete perineal shave	1.4	4.6	86.3
Partial or mini-shave	56.2	13.3	29.5
Enema in early labor	43.4	24.5	30.9
Epidural or caudal anesthesia	8.2	42.4	48.4
Hypodermic analgesics in labor	31.5	57.8	8.6
Practice	*Encouraged/ Permitted Routinely (%)*	*Permitted Except When Contraindicated (%)*	*Discouraged/ Not Permitted (%)*
Ambulation in labor	44.2	47.0	8.2
Labor in patient's most comfortable position	76.9	22.1	0.4
Presence of father throughout labor	95.2	4.8	...
Presence of coach or other support person	85.7	10.8	3.4

*Percentage of respondents who did not respond to each item not shown.

courage or routinely permit, perform or order the practices and procedures included in the survey, statistically significant differences were apparent in the responses of physicians younger than 40 years and those aged 60 and older with respect to many of the items (Table 3). Younger physicians were found to be significantly more likely than their older colleagues to forgo routine preps, enemas and episiotomies, and to embrace a variety of the nontraditional, alternative birth practices. The difference is perhaps most striking in the acceptance of hospital-based alternative birth areas and early hospital discharge. The proportion of physicians in the youngest age group who encourage or routinely permit these two practices exceeds those of respondents in the oldest age group by factors of three and four, respectively.

Discussion

Since a comparable survey of obstetrical practices 10 or 20 years ago is not available and little empirical data exist on the current prevalence and use of alternative birth practices and settings, it is not possible to compare the results of this survey with previous research. Anecdotal indications suggest that, in the past, many or most obstetricians simply followed routines—for example, complete prep on admission, enema in early labor, sedation and the like. Patients rarely requested

TABLE 2.—*Prevalence of Selected Birth Practices* (N = 502)*

Practice	*Encouraged/ Permitted Routinely (%)*	*Permitted on Request (%)*	*Discouraged/ Not Permitted (%)*
Presence of father at normal birth	92.4	6.2	1.0
Presence of other support person(s) at normal birth	40.7	42.0	16.4
Presence of father at primary nonemergency cesarean birth	70.5	19.7	9.0
Presence of siblings at normal birth	6.0	32.7	60.3
Assistance of mother in delivery of infant	42.7	21.7	30.8
Assistance of father in delivery of infant	9.6	29.5	58.6
Delivery without stirrups	11.6	56.4	29.7
Cutting of umbilical cord by father	24.7	42.4	29.6
Holding of infant by mother following birth	89.8	9.4	0.2
Holding of infant by father following birth	84.8	11.0	1.8
Attempted breast feeding in delivery room	44.9	44.6	10.2
Dimmed lighting in delivery room	25.7	48.2	25.3
Taking of photographs	65.9	29.1	4.2
Early postpartum parent-infant interaction (bonding)	91.6	7.2	0.2
Discharge within 6-12 hours	15.2	58.8	25.7
Delivery in hospital-based alternative birth area	26.5	48.8	22.1
Delivery in freestanding alternative birth center	2.6	6.6	85.4
Attendance at home birth	0.2	1.0	98.2

*Percentage of respondents who did not respond to each item not shown.

TABLE 3.—*Percentage of Respondents Who Encourage or Routinely Permit, Perform or Order Selected Obstetrical Practices or Procedures,* by Age Group*

Practice or Procedure	*All Respondents† (N = 502) (%)*	*Age Group*			
		Under 40 (N = 103) (%)	*40-49 (N = 153) (%)*	*50-59 (N = 149) (%)*	*60 and Older (N = 91) (%)*
Partial or mini-shave	56.2	43.7	52.9	59.7	69.2
Enema in early labor	43.4	33.0	43.8	44.3	53.9
Presence of coach or other support person (other than father) throughout labor	85.7	95.2	93.5	79.9	71.4
Delivery in labor bed (planned)	15.5	24.3	17.0	10.7	9.9
Delivery without stirrups	11.6	21.4	10.5	9.4	6.6
Delivery in hospital-based alternative birth area	26.5	43.7	30.7	16.8	14.3
Presence of support persons(s) (other than father) at birth	40.7	52.5	46.4	32.2	30.8
Presence of father at cesarean birth	70.5	83.5	68.0	71.1	58.3
Episiotomy in primigravidas	78.1	66.0	76.5	82.6	86.9
Episiotomy in parous parturients	47.6	35.0	41.8	53.7	61.6
Cutting of umbilical cord by father	24.7	43.7	22.2	18.1	17.6
Dimmed lighting in delivery room	25.7	36.9	26.8	19.5	19.8
Taking of photographs	65.9	74.8	68.6	62.5	56.1
Holding of infant by father following birth	84.8	89.3	88.3	85.2	73.6
Early postpartum parent-infant interaction (bonding)	91.6	98.1	94.8	92.0	78.0
Early skin-to-skin contact between mother and newborn	76.9	83.5	79.7	77.2	65.9
Discharge within 6-12 hours	15.2	21.4	19.0	12.7	5.5

*Selected practices or procedures for which responses of physicians younger than 40 years and those of physicians age 60 and older were found to differ significantly at $P < .05$ using two-tailed test.
†Includes respondents whose age is unknown, not shown separately.

variations and, when they did, such requests were likely to be denied.

The stereotype of the paternalistic, autocratic obstetrician, cited disparagingly by some feminists in recent years, would be difficult to support in light of the present survey findings. The image of contemporary obstetrical care as an impersonal, high-technology clinical enterprise devoid of human, caring regard for the childbirth process is similarly unsupported by these data. The results of the survey suggest that a major reassessment of obstetrical practice has occurred and that today's practicing obstetricians, if not encouraging or routinely employing practices that minimize the dehumanizing aspects of the application of high technology to childbirth, are at least willing for the most part to accommodate the preferences of patients and families for a more "high-touch" birth experience. The general attitude reflected here appears to be that if a patient's request does not prejudice the safety of the mother or infant, it is reasonable to honor it.

The results suggest further that this evolution of obstetrical practice patterns is still in process, as evidenced by the greater propensity of younger physicians to encourage, permit or utilize alternative birth practices and settings. As more young obstetricians enter practice, it seems likely that the "high-touch" approach to obstetrical care will increasingly represent the norm. Moreover, as women continue to enter the medical profession in increasing numbers, their presence may accelerate this change. Although the number of women in the responding sample was too small to permit adequate statistical confidence in gender comparisons, their responses nevertheless suggest a more lenient attitude toward certain birth options than among even physicians in the youngest age group. More than 40% of the women, for example, said they *encourage* delivery in a hospital-based alternative birth area, while among all physicians younger than 40 the proportion was less than one in three and among all responding physicians was barely one in six.

Although the results clearly suggest a growing acceptance of alternative birth practices, the data also indicate that use of alternative birth *settings* has not been as widely accepted. While delivery in hospital-based alternative birth areas is encouraged or permitted by the majority of respondents, uniformly large proportions of respondents in each age (and sex) group continue to regard deliveries in freestanding birth centers or at home as unacceptable alternatives. With respect to freestanding centers, it should be noted that the survey did not inquire about whether such facilities actually existed in respondents' communities, and it is possible that some respondents simply checked "not permitted or performed" for lack of a more appropriate response alternative. Home birth, on the other hand, is an option in every community; in this case, it may be that the lack of technological support for rapid, effective response to unpredictable complications, with attendant risks, has discouraged most obstetricians from honoring such a request. Concern for the safety of the mother and infant, as well as the liability risk inherent in deviations from norms of clinical practice, may play a major role in discouraging wider acceptance of other birth alternatives as well. The assistance of fathers in deliveries and early hospital discharge are examples of practices that may pose intolerable medicolegal risks for both physicians and hospitals in an area of medical practice that has already experienced an enormous increase in malpractice litigation. Professional liability exposure may in fact pose one of the greatest obstacles to the further integration of alternative birth practices into routine clinical practice.

The explanation for the changing obstetrical practice patterns indicated by these results is not entirely clear. While it seems likely that the women's movement and a general trend toward greater patient autonomy have played roles in causing a reassessment of traditional attitudes and practices in obstetrics, it may also be true that the changes reflect physicians' own desires to mitigate the dehumanizing aspects of the technological advances that have helped produce the dramatic improvements in maternal-fetal health in recent decades. DeVries[2] has suggested that medical interest in providing birth options has been stimulated by new market demands, in which case the data may reflect the broader economic issue of increasing competition in the health services marketplace, both among traditional providers and between traditional and nontraditional providers of obstetric care. In any event, the perceived need for a "high-touch" approach to counterbalance the "high-tech" aspects of obstetrics is clearly being addressed.

Findings of this study suggest above all the need for further research in this area. Studies are needed to assess the attitudes and practices of a more representative population of obstetricians—as well as those of general and family practitioners who deliver babies—and to explore factors influencing the prevalence and use of birth alternatives, such as the availability of alternative settings, consumer demand, hospital administrative policies, professional liability concerns and physician-patient relationships. Analysis of such variables will yield a better understanding of the role of ecological, socioeconomic and interpersonal factors in changing practice patterns and may enable an understanding of how the future needs of all health care consumers can be better met.

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Doctor Bethune Served the People

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What if there were a Westerner who was a hero to hundreds of millions of Chinese? What if Mao Zedong had eulogized him as a model of selfless devotion and technical expertise? What if that man had named in his honor an International Peace Hospital and a military medical school and, dedicated to his memory, two tombs in the People's Republic of China? And what if he had been a thoracic surgeon who died serving the people of China? Would you be intrigued enough to want to know more about him? I was.

Norman Bethune was born in 1890 and was raised in Ontario, Canada, the son of religious parents. Much has been written about the difficulty of growing up a clergyman's child, but about his forebears, Bethune said, "On my mother's side, I'm an evangelist. On my father's side, I have a compulsion to do, to act."[1] He demonstrated these traits after his second year of college by serving one winter in the Frontier College. Established in 1899, its purpose was (and is) to provide basic education to the laborers of Canada. But the teacher himself had to work alongside the workers he taught, ten hours a day, six days a week. In addition to instructing them each evening, he had to establish a library and conduct a Sunday service. There exists a photograph of Bethune standing proudly among the lumberjacks he both worked with and taught.[2]

World War I erupted after Bethune had completed his second year of medical school at the University of Toronto and he immediately enlisted. He was sent to France in a medical unit as a stretcher-bearer. There and in Flanders he witnessed up close the appalling carnage and terrible waste of trench warfare. At the second battle of Ypres, with the Canadians going down in waves, he himself was severely wounded. Weak from loss of blood, he survived the slow and difficult evacuation of the injured to the rear before medical care was available. He never forgot the experience. After six months in hospitals, he was sent home where he completed his medical studies.

He reenlisted, but this time as a junior medical officer in the Royal Navy, and served 14 months on the aircraft carrier HMS Pegasus. After demobilization, he went to London to complete his surgical training. Like many disillusioned by the war, he became committed to art both as a faith and a form of therapy. He began to paint and write poetry, activities that he would continue during most of his life. While sitting for the examination to become a fellow of the Royal College of Surgeons, he met a young Scottish woman whom he later married. They traveled about Europe for six months, honeymooning and observing surgical procedures in some of the best centers of the day. Finally, at age 34, he decided it was time to practice and chose an opportunity in Detroit, then in a postwar boom.

He set up an office in what he later discovered was the motor city's red-light district. Except for the prostitutes, however, most of his patients were unable to pay for his services and he received fees in the form of food or furniture. He came to recognize the connection between disease and socioeconomic condition. Finally, one of the established surgeons invited him to become a partner and he began to prosper. While working long hours, he became increasingly irritable, emaciated and an insomniac. Long a smoker, his cough became worse until one day he arrived home expelling blood clots into a handkerchief. He had tuberculosis involving his entire left lung. He told his wife, "I'm finished."

In 1926 the mainstay of treatment for tuberculosis was still isolation and bed rest in a sanatorium when possible. He went first to one in Ontario and then to the famous Trudeau sanatorium in upstate New York. There he joined three other afflicteds, including Alfred Blalock, in a cottage on the slopes of Mt Pisgah. Though hopeful, each was resigned to his eventual demise. Bethune spent his time reading and painting on the walls of the cottage a mural which depicted nine stages in the progress of tuberculosis, ending with the patient in the arms of the Angel of Death.[3]

Then one night he picked up a book entitled *The Surgery of Pulmonary Tuberculosis* and began to read. He sat up, startled. The author, a Dr John Alexander, stated that many formerly hopeless cases like his could be cured by collapsing a lung. Soon he went to the administration and demanded a pneumothorax. A little over two months later, he jubilantly left the sanatorium with negative sputum. At 38 he had been raised from the dead. Thereafter he vowed to devote his life to the treatment and cure of tuberculosis.

After three months of basic research, he joined Dr Edward Archibald, recognized in his lifetime as the father of thoracic surgery, at the Royal Victoria Hospital in Montreal. There he worked assiduously to build up the clinic and service for patients with tuberculosis. While operating, teaching and publishing scholarly articles, he designed or improved a

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number of surgical instruments including the "iron intern," a form of which is still used today.[4] He pioneered several techniques in the treatment of tuberculosis, including talc poudrage and the use of maggots to treat empyema. Finally, he was invited to be chief of service at the Sacre-Coeur Hospital near Montreal.

During this period, he began to paint oils and his work includes portraits of himself, his wife and one entitled *Night Operating Theater*. He helped to found and support a Children's Art Center to help children develop their creativity. Meanwhile, he became aware again of the close relationship between the disease he was combating and the socioeconomic conditions of his patients. He often could not bear to discharge those he had cured, knowing that they would return to the same environment in which they had acquired their diseases. Though he started a free clinic for the unemployed, something more had to be done about medical care in Quebec.

To Serve the People. Motto of the Chinese Medical Service.

After a visit to the Soviet Union to attend a congress in 1935, he returned to organize a group to develop a health care plan for the province. The Bethune group, consisting of doctors, dentists, nurses, social workers and an actuary, proposed a plan, or rather four plans, for providing health care to the people of Montreal. The idea was to experiment to find the best and most practical means of achieving comprehensive care. Because in the middle of the Great Depression the capitalist system seemed a complete failure to many people, he joined the Communist party as a symbol of his commitment to social reform.

Then, in 1936, something of even greater import to him occurred—the outbreak of civil war in Spain. Franco, attempting to overthrow the elected government and restore a monarchy, was abetted for their purposes by Mussolini and Hitler. Most of the military doctors had joined the rebels against the republic.[5] Help was needed, and Bethune and others, including volunteers of the International Brigades, responded. Fighting on the Loyalist side, Eric Blair, better known as George Orwell and author of *1984*, was shot through the neck.[5] Fortunately, he lived to write about it in his *Homage to Catalonia*.

In Spain, Bethune made his greatest innovation—a mobile blood transfusion service for the wounded. He and his associates collected blood from donors and transported it to the front or to hospitals. He knew from his own experience how important it was to replace blood quickly in order to prevent shock and death. He trained personnel and organized other teams in this advance in military medicine.

But the war was not going well for the Republican side. While the democracies, including the United States, blockaded the Republican government, the fascists made Spain a proving ground for other innovations such as aerial bombing of civilian populations and blitzkrieg. Ill-equipped and disorganized, democratic Spaniards were losing. Though he still hoped, Bethune became increasingly disillusioned and bitter and drank more. Finally, he turned over his transfusion service to the Spanish Ministry of War and began organizing camps for refugee children. He was asked to return to Canada to raise funds for the Republican cause. In the month before he left, he made a film entitled *Heart of Spain* describing what was happening there as a rehearsal for the wider war to come. Traveling across Canada and the United States, he appealed for support to make Spain the tomb of fascism. Back in Montreal, he sent off the funds he had collected, but now a new crisis had developed on the other side of the globe—the Japanese had invaded China. The China Aid Council of New York asked him if he would go. He agreed because, in his view, it was the same fight as the one in Spain, only the Chinese needed help even more.

With supplies and colleagues, he sailed from Vancouver for Hong Kong on January 8, 1938. For three long months after his arrival, he evaded and circumvented the enemy to reach Yenan, the refuge of the Chinese Communists. After their 6,000-mile fighting retreat, the epic Long March, there in the northern provinces the 8th Route Army was resisting the Japanese invaders. While Bethune operated, he assessed the situation in the light of his past experience. Meeting with

Zhou Enlai and Mao, he explained what he believed needed to be done (Mao Zedong, "In Memory of Norman Bethune," Dec 21, 1939). He wanted to take a surgieal field hospital on mules right to the soldiers and partisans fighting in the rugged countryside of Hopei. Everyone who listened thought it too risky, but Bethune insisted and was permitted to go. He set out aeeompanied by another doetor (soon to leave), a nurse and an interpreter. His eall to others was, "Doetors, go to the wounded."

Now followed the amazing final ehapter in the life of this remarkable man. During the next 18 months, he earried out hundreds of operations, many just behind the battle lines, without rubber gloves and sometimes without anesthesia. His experienee and skills made him an exeellent eombat surgeon, but that was not all. He organized a model hospital while training medical personnel from orderlies to doetors. In the absenee of trained personnel or sehools, it was neeessary to turn peasants and workers into nurses and doetors, a proeess that the Chinese continued after the patriotie and civil wars.[6] He gave leetures and wrote training manuals and textbooks while riding up to 30 miles a day. Everywhere he went he set an example of unstinting labor for and devotion to the patients. He even eontributed his salary to provide small eomforts for them. And, ultimately, he died while serving them. From his letters, moreover, it appears that he was a happy man in this last period of his life. Alone in a strange country, he had at last found joy and peace in serving the people. The Chinese ealled him Pai Chu En—White Seek Graee—honored as no other Westerner. He is, indeed, the world's best-known surgeon.[7]

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Book Reviews

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

MONITORING IN ANESTHESIA AND CRITICAL CARE MEDICINE—Edited by Casey D. Blitt, MD, Attending Anesthesiologist, Tucson Medical Center, El Dorado Medical Center and Northwest Hospital, and former Professor of Anesthesiology, University of Arizona College of Medicine, Tucson. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 707 pages, $79.

This multiauthored textbook contains 28 chapters devoted to providing a complete "state-of-the-art" text on monitoring in anesthesia and critical care medicine. The book is divided into six sections—general principles, cardiovascular care systems, respiratory system, central nervous system, miscellaneous and anesthetic subspecialties. Although nearly every conceivable, currently used monitoring approach is described, the emphasis is clearly on anesthesia rather than critical care medicine.

As with any multiauthored text, the chapters vary in intensity, length and quality. Technically, the large print and illustrations make the book easy to read. Most of the authors are leading authorities in their respective fields. As a result, most of the chapters represent in-depth analyses of each form of monitoring, especially the chapters on central venous pressure, invasive blood pressure and respiratory monitoring. There is only a modest amount of overlap among chapters, which is unusual in a multiauthored text. This certainly is a credit to the editor.

That books frequently are not up-to-date when published partly applies to this text. In most chapters, the most current reference is 1982. Not surprisingly, many of the chapters are not "state-of-the-art" in their descriptions of monitoring techniques, particularly in electrocardiography, neuromuscular monitoring, blood gas analysis and computers. The computer chapter is especially weak in view of how rapidly computer science is evolving, especially in critical care medicine.

While this text is excellent with the technical and medical aspects of monitoring, this reviewer was disappointed that a greater emphasis was not placed on a cost-benefit analysis. For example, recognizing the high expenditure of funds and resources for monitoring, how much has patient care been enhanced from an outcome point of view? The chapter entitled "The Swan-Ganz Catheter: Past and Present" by Swan and Ganz is especially disappointing in this regard. Conversely, Dr Vandam's chapter "The Senses as Monitors" is particularly refreshing in emphasizing the value of basic monitoring in anesthesia. In an atmosphere of cost-containment, overall improved outcome needs to be equated (or not equated) to the use of sophisticated, expensive monitoring; that was not adequately done in this text.

Overall, this text represents a modest description of monitoring for critical care medicine. It is highly recommended, however, for those wishing information regarding perioperative monitoring.

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COMPREHENSIVE MANAGEMENT OF RESPIRATORY EMERGENCIES—Edited by Barry E. Brenner, MD, PhD, Assistant Director, Emergency Medicine Center, UCLA Hospital and Clinics, and Assistant Professor of Medicine, UCLA Center for Health Sciences, Los Angeles. Aspen Publishers, Inc, 1600 Research Blvd, Rockville, MD 20850, 1985. 386 pages, $61.50.

This book, containing 20 chapters and written by a number of authors, reviews a variety of urgent respiratory problems and diseases frequently encountered in emergency rooms. The major topics include thoracic trauma, respiratory failure, pneumonia, chronic obstructive pulmonary disease, asthma, acid-based abnormalities, pulmonary edema and embolism, inhalational disorders, high altitude pulmonary edema, decompression sickness, chest radiology, the neonatal airway, oxygen therapy and procedures involving the upper airway and thorax. The chapters generally provide in-depth clinical discussion as well as practical approaches to the management of these respiratory disorders. The majority of chapters contain helpful tables and instructive figures. The chapters are completed with reference lists containing from 36 to 362 citations.

Some shortcomings are evident. The sequence of chapter topics might have been better organized for reading continuity—for example, related conditions (such as chronic obstructive pulmonary disease and asthma) could have been placed next to each other rather than several chapters apart. Discussions of pneumothorax, hemothorax, pneumonia and pulmonary edema were repeated in several chapters by different authors; however, varied perspectives sometimes may be desirable. Despite a comprehensive approach the book lacks adequate discussion about respiratory muscle fatigue, diagnostic studies of the lower extremities in the diagnosis of pulmonary thromboembolism, drowning and drug overdose. A chapter on the radiologic appearance of specific pneumonias did not include any chest radiographs.

Overall, I believe that this book is an excellent textbook for physicians in the emergency department and critical unit. The chapters are generally well written and concise and provide the essential information about appropriate topics. This reference work accomplishes its general goal of supplying experienced physicians with more of a comprehensive and accurate review of the literature rather than does a manual-style collection of practical recipes and techniques.

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COMPREHENSIVE REVIEW IN TOXICOLOGY—Peter D. Bryson, MD, Medical Director, Poison Treatment Center, Emergency Medicine Staff, St Anthony Hospital Systems, Denver. Aspen Publishers, Inc, 1600 Research Blvd, Rockville, MD 20850, 1986. 329 pages, $33.

Aspen Publications has produced a 300-page review of toxicology by a single author, Peter D. Bryson, MD, who is the medical director of the Poison Treatment Center at St Anthony Hospital Systems of Denver. This $33 text has 16 chapters dealing with broad areas of toxicology. The author intends the text to be used by clinicians involved in the management of poison patients, and intends the text to be both comprehensive and practical. This easily readable text partially meets these goals. It is evident that this text grew out of a series of lectures that have been transformed into a book. The tables are almost exclusively materials explained in the text and add little to the ease of understanding the data presented. Introductory chapters on pharmacokinetics and toxicokinetics as well as the general management of the overdoses are straightforward. The text is especially useful in that it is written by one author in a uniform style. Unfortunately, the author mentions controversial areas and rarely reviews them in detail. Although there are detailed references and suggested readings, most of these are from the 1970s or early 1980s. In the final analysis, the real question is whether this text would be preferred over more detailed reviews that are published in multiauthored texts by Winchester or Goldfrank. When compared with these texts the subjects covered are in general treated more superficially. Because of the uniform style and easy readability, however, this text does serve a useful purpose for those readers anxious to learn the basics of clinical toxicology.

CHARLES E. BECKER, MD
Professor of Medicine
University of California, San Francisco, School of Medicine

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OTOLOGIC RADIOLOGY, WITH CLINICAL CORRELATIONS—Ramon Ruenes, MD, Professor of Radiology, National Autonomous University of Mexico, and Director, Center for Head and Neck Radiology, Mexico City, and

Antonio De la Cruz, MD, Director of Education, House Ear Institute, and Associate Clinical Professor of Otolaryngology, University of Southern California School of Medicine, Los Angeles. Macmillan Publishing Company, 866 Third Ave, New York, NY 10022, 1986. 183 pages, $49.95.

This comprehensive and timely work on otologic radiology combines the insights of a radiologist (Dr Ruenes) and an otologist (Dr De la Cruz). The text thoroughly addresses many of the major advances which have taken place in the radiographic evaluation of the ear and temporal bone in recent years without neglecting more traditional examination techniques. Coverage ranges from conventional plain film and polytomographic examination to recent innovations such as computed tomography and magnetic resonance imaging. The diagnosis-oriented format facilitates quick reference in a busy clinical setting without detracting from the book's use as an advanced textbook in the field. Numerous illustrative radiographs of both normal and pathologic anatomy are included. Images have generally been reproduced with excellent quality which is further enhanced by the frequent use of line drawings to accentuate key features in the regions of interest. This text should be of use to both practicing otologists and radiologists who are called upon to interpret temporal bone studies.

ROBERT K. JACKLER, MD
Assistant Professor of Otolaryngology
University of California, San Francisco, School of Medicine

* * *

CLINICAL RADIOLOGY OF THE SPINE AND THE SPINAL CORD—Mohamed Banna, MB, BCh, MD, FRCR, FRCP(C), DABR, Professor of Radiology, McMaster University Medical Center, and Chief of Neuroradiology, Chedoke-McMaster Hospitals, Hamilton, Ontario, Canada. Aspen Systems Corporation, 1600 Research Blvd, Rockville, MD 20850, 1985. 449 pages, 1,047 illustrations, $78.

This textbook on the spine and spinal cord is probably the best compendium of radiographic and clinical knowledge available. The book contains 11 chapters: "Normal Spine," "Developmental Anomalies of the Spine," "Introduction to Myelography and Computer Tomography," "Spinal Fractures and Dislocations," "Intervertebral Disc," "Intraspinal Mass Lesions," "Spinal Dysraphism," "Tumors and Tumor-Like Lesions of the Vertebral Column," "Spinal Deformities," "Miscellaneous Conditions" and "Magnetic Resonance Imaging."

The book is well organized, well written and concise. The quality of the illustrations is excellent and the many line drawings are outstanding. Great care has been taken by the author in labelling the pictures, and anatomical structures and pathology are readily apparent. The volume also updates established references such as *CT of the Spine* by Haughton and Williams and *CT of the Spine* by Donovan Post.

Compared with the book *CT of the Spine and Spinal Cord* edited by Newton and Potts, this textbook is easier to read and reaches the same high standard of excellence from the standpoint of organization and illustration. It is a welcome addition to the spine literature and is recommended enthusiastically.

NICOLE-FR. BOLENDER, MD
Department of Radiology
University of Washington
Seattle

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STATE OF THE ART REVIEWS: OCCUPATIONAL MEDICINE—The Microelectronics Industry: January-March 1986, Vol 1, No. 1—Guest Editor: Joseph LaDou, MD, Acting Chief, Division of Occupational and Environmental Medicine, University of California, San Francisco. Hanley & Belfus, Inc, 210 South 13th St, Philadelphia, PA 19107, 1986. 197 pages, single copies $22. The subscription price is $48 per year (US), $56 outside US (add $12 for surface, $20 for air mail).

This volume is the first in a series of quarterly reviews on a variety of important occupational medicine topics. This flagship book augurs well for the series. It identifies current and potential problems in the microelectronics industry, proposes some solutions and, most important, calls for research in this burgeoning but vexing area. The topics covered are very important and include sections on the toxicology of substances used in the industry as well as musculoskeletal problems associated with it.

Authors of chapters are experienced, and the writing is clear. Even the summaries in the Table of Contents and headings scattered through the chapters are helpful for a quick browse. The bibliographies are generally short. This reflects sad deficiencies in research regarding medical problems associated with the microelectronics industry.

On the down side, it is unfortunate that some assertions are made on the basis of unpublished data or unreferenced studies. This, however, reinforces Dr LaDou's foreword: "No major study on the health of American high technology electronics workers has been conducted. . . ." One area not addressed is that of occupational demands and tensions. These are common problems in an industry with high turnover, financial uncertainties and enormous cultural and educational differences between managers/inventors and line workers.

Overall, this publication is extremely important for any physician's bookshelf if the physician sees patients who work in the microelectronics industry or who are neighbors of such installations. In addition, it is a readable and digestible reference for any person interested in the inner, arcane workings of one of our most important industries.

LINDA HAWES CLEVER, MD
Chairman
Department of Occupational Health
Pacific Medical Center
San Francisco

* * *

ATLAS OF GYNAECOLOGICAL DIAGNOSIS—Abdel Fattah Youssef, Professor and Ex-Chair, Department of Obstetrics and Gynaecology, Cairo University; Senior Gynaecological Surgeon, Kasr El Aini Hospital, Cairo. Churchill Livingstone, 1560 Broadway, New York, NY 10036, 1984. 179 pages, $32.

The major strength of this atlas is the beautiful pictures depicting a wide variety of vulvar, vaginal and cervical pathology. The photographs are excellent and provide typical findings in the specific entities. In this respect, the book should be very useful to medical students and residents as they first learn about these conditions. On the other hand, I was a bit disappointed in the sections on adnexal pathology, laparoscopy and ultrasound. It would have been nice if the authors had carried the theme of the book through these sections and furnished a wider variety of pictures of the pathologic conditions involved in each. In spite of these shortcomings, however, what is presented is very worthwhile and fledgling gynecologists will probably find the atlas very useful.

MORTON A. STENCHEVER, MD
Department of Obstetrics & Gynecology
University of Washington
Seattle

* * *

SCIENTIFIC BASIS OF OBSTETRICS AND GYNAECOLOGY: Third Edition—Edited by Ronald R. Macdonald, MD, FRCS(Ed), FRCOG, Consultant Obstetrician and Gynaecologist, The Hospital for Women and Children, The General Infirmary, and Senior Clinical Lecturer in Obstetrics and Gynaecology, University of Leeds, United Kingdom. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036. 514 pages, $59.

Scientific Basis of Obstetrics and Gynaecology by Dr Ronald Macdonald is an interesting departure from the standard textbook. The chapter topics are not those usually seen in a typical textbook, yet they incorporate many ideas and concepts of related areas into a single topic area. In the preface, the author indicates the purpose of the book is to "discuss selected topics in depth from the basic principles through new information to the clinical application." In this respect, the book is a success. Each chapter is essentially a monograph of the topic. The text will be especially valuable to those who have been away from their training for several years and need to upgrade their knowledge in one of the 14 areas. The drawback to the book is that it only covers a limited number of topics. As I finished reading it, my desire—as with that of a good novel—was to eagerly await the sequel.

RALPH W. HALE, MD
Professor and Chairman
Department of Obstetrics and Gynecology
John A. Burns School of Medicine
University of Hawaii
Honolulu

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(Continued from Page 37)

Medical Education Committee. PO Box 10905, Eugene 97440.

Salem Hospital, 665 Winter St SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St SE, Salem 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St SE, Salem 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St Vincent Hospital & Medical Center, 9205 SW Barnes Rd, Portland 97225. (503) 297-4411, Ext 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept of Psychiatry, Oregon Health Sciences University, Portland 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept of Medicine, Oregon Health Sciences University, Portland 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland 97201. (503) 225-7590.

EMERGENCY MEDICINE

October 23-24—**Pediatric Advanced Life Support.** Portland. Thursday-Friday. Red Lion Motor Inn/ Portland Center. Contact: OHSU-CME.

FAMILY PRACTICE

October 23-25—**Pacific Northwest Review of Obstetrics and Gynecology.** See below.

OBSTETRICS AND GYNECOLOGY

October 23-25— **Pacific Northwest Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion Motor Inn/Jantzen Beach. Contact: OHSU-CME.

PEDIATRICS

October 23-24—**Pediatric Advanced Life Support.** Portland. Thursday-Friday. Red Lion Motor Inn/ Portland Center. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

July 14-16—**Plastic Surgery for the Primary Care Physician.** Sunriver Resort. Monday-Wednesday. Contact: OHSU-CME.

July 17-18—**Dermatology for the Non-Dermatologist.** Sunriver Resort. Thursday-Friday. Contact: OHSU-CME.

September 5-6—**The Ashland Conference: Endocrinology.** Ashland. Friday-Saturday. Ashland Hills Inn. Contact: OHSU-CME.

October 10-12—**The Salishan Conference: Cardiology.** Gleneden Beach. Friday-Sunday. Salishan Lodge. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

(Continued on Page 136)

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MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

July 13-18—**Summer Update in Clinical Microbiology and Immunology** (Sponsor: University of Utah). Sunday-Friday. Jackson Hole, Wyoming. 23 hrs. Contact: John Matsen, MD, (801) 581-7480.

July 25-26—**Diabetes Update** (Sponsor: UUMC). Friday-Saturday. Utah State University, Logan. 8 hrs. Contact: Chuck Hand, (801) 363-3024.

September 4-5—**Postgraduate Laser Program—GI.** (Sponsor: UUMC). Thursday-Friday. University of Utah Medical Center, Salt Lake City. 10 hrs. Contact: John Dixon, MD, (801) 581-2256.

September 10-12—**Utah State Medical Association Annual Meeting.** Wednesday-Friday. Yarrow Holiday Inn, Park City. Contact: USMA, 540 E Fifth South, Salt Lake City 84102. (801) 335-7477.

September 12-13—**Attention Deficit Disorder in Children and Adults** (Sponsor: UUMC). Friday-Saturday. Snowbird Resort. 6 hrs. Contact: Paul Wender, MD, (801) 581-8664.

September 19-20—**Postgraduate Laser Program—GYN** (Sponsor: UUMC). Friday-Saturday. University of Utah Medical Center, Salt Lake City. 10 hrs. Contact: John Dixon, MD, (801) 581-2256.

September 25-26—**Postgraduate Laser Program—Urology** (Sponsor: UUMC). Thursday-Friday. University of Utah Medical Center, Salt Lake City. 10 hrs. Contact: John Dixon, MD, (801) 581-2256.

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143, (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

October 6-8—**Occupational Low Back Pain** (Sponsor: UUMC). Monday-Wednesday. Snowbird Resort. 15 hrs. Contact: Connie Crandall, (801) 581-3841.

October 31-November 1—**Stress, Emotion and Heart Disease** (Sponsor: UUMC). Friday-Saturday. Marriott Hotel, Salt Lake City. 15 hrs. Contact: Hilmon Castle, MD, (801) 581-8664.

November 7-8—**Advanced Trauma Life Support** (Sponsor: UUMC). Friday-Saturday. Quality Inn, Salt Lake City. 16 hrs. Contact: Carla Holmes, (801) 533-6608.

November 20-21—**Postgraduate Laser Program—GI.** (Sponsor: UUMC). Thursday-Friday. University of Utah Medical Center, Salt Lake City. 10 hrs. Contact: John Dixon, MD, (801) 581-2256.

January 5-14—**Hip and Knee Bioskills Workshop** (Sponsor: UUMC). 10 days. Snowbird Resort. 15 hrs. Contact: Aaron Hoffman, MD, (801) 581-8664.

January 20-22—**Pulmonary Function Testing** (Sponsor: UUMC). Tuesday-Thursday. RMCOEH, University of Utah Medical Center. 18 hrs. Contact: Connie Crandall, (801) 581-8719.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

July 23—**The Burn Wound.** Seattle. Wednesday. Westin Hotel. Contact: U/W.

July 24-25—**The Burn Patient.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

July 24-27—**Anesthesiologists 1986 Seafair Meeting.** Seattle. Thursday-Sunday. Seattle Sheraton. Contact: WSMA.

July 31-August 2—**Reproductive Endocrinology.** Seattle. Thursday-Saturday. U/W Health Sciences Building. Contact: U/W.

August 7-8—**Sports Medicine for Primary Care Physicians.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

(Continued on Page 140)

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NEPHROLOGIST WANTED. Join group Nephrologists in Central California. Acute and chronic hemodialysis facilities available. Salary negotiable. Reply to Number 122, The Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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FAMILY OR GENERAL PRACTICE PHYSICIAN needed for an innovative primary health care system. Excellent salary, fringe benefits and continuing educational opportunities. Write to PO Box 3239, Farmington, NM 87499.

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SAN FRANCISCO BAY AREA—Director, Department of Anesthesia. Community Hospital, a 145-bed acute care teaching facility owned by Sonoma County and managed by National Medical Enterprises, Inc., is seeking a BC/BE Anesthesiologist with extensive clinical experience and demonstrated management ability. Located 60 miles north of San Francisco in the heart of the wine country, the hospital is affiliated with the UC School of Medicine and offers a nationally recognized three year Family Practice Medicine Residency Program as well as a full range of services from a Level-2 ICN to Outpatient Clinics. Send CV by 8/1/86 to: Search Committee, c/o Office of the Administrator, Community Hospital, 3325 Chanate Rd., Santa Rosa, CA 95404. EOE/AA.

GENERAL INTERNIST: Excellent professional opportunity. Internal Medicine associate to join solo practitioner in rapidly expanding rural area of Northern San Diego County. Less than one hour drive from San Diego. Send CV, ASAP to S. Michael Roche, MD, 591 E. Elder, Ste. C, Fallbrook CA 92028; (619) 723-1101.

PART-TIME POSITIONS available for qualified, experienced physicians in busy suburban Emergency Department. Excellent access to consultative services. San Francisco Bay area. Contact T. Del Presto, MD, Chief, Emergency Department, Kaiser Foundation Hospital, 1150 Veterans Blvd., Redwood City, CA 94063 or call (415) 780-2208.

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PULMONOLOGIST—Southern California. Oualified Pulmonary Internist to join solo certified Pulmonologist in predominantly specialty practice. Attractive location. Contact Pulmonary Position, PO Box 4110, Seal Beach, CA 90740.

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MEDICAL DIRECTOR—Emanuel Hospital, Portland, Oregon, is seeking board certified MD applicants for a Medical Director to oversee the medical management of this tertiary facility. The position has been vacant for four years and will require a dynamic, goal oriented individual willing to create a positive environment for medical practice in a highly competitive market. Emanuel operates a level one trauma center, air ambulance, acute rehabilitation facility, regional burn center, and has a major commitment to women's and children's medicine, cardiology and oncology. Contact: Search Committee, c/o Robert Forman, Vice President, Human Resources, Emanuel Hospital, 2801 N. Gantenbein, Portland, OR 97227. Member HealthLink and Health Network of America. Equal Opportunity Employer.

ORTHOPAEDICS—Private practice opportunity in Espanola, New Mexico. Financial assistance with income guarantee. Easy access to all forms of recreation—just 20 miles north of Santa Fe. For further information, please submit CV to: Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or, call 1-800-545-4030, Ext. 8300.

BOARD CERTIFIED FAMILY PHYSICIAN OR GENERAL INTERNIST needed for multispecialty group in Durango, Colorado; Contact Bonnie DuPuis, PO Box 2637, Durango, CO 81302 or Call (303) 247-2611.

PACIFIC NORTHWEST: Beautiful Coeur d'Alene, Idaho, the capital of the Inland Northwest's extensive network of pristine lakes, is in immediate need of a staff physician to join Group Health Northwest, a family practice staff model HMO, now expanding into North Idaho. Excellent benefit package, association with the 24 physicians of Group Health of Spokane, adequate call sharing, vacation and CME coverage, but with the independence of a small practice in a beautiful lakeside town which has a hospital and most specialties represented. Board certified FP's with OB experience desired. Contact Thomas Kearney, Group Health of North Idaho, PO Box 5339, Coeur d'Alene, ID 83814.

CARDIOLOGIST, INVASIVE—150-physician, multispecialty, prepaid group located in the San Francisco Bay Area wishes to add another Cardiologist/Internist. Practice includes large volume of referrals for invasive procedures. Doppler-echo skills required. University affiliation available. Please contact: E. Andrews Neal, MD, The Permanente Medical Group, Inc., 260 International Circle, San Jose, CA 95119; Telephone (408) 972-6340.

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PHYSICIAN COORDINATOR, Emergency Department/Prompt Care Center, Saint Cabrini Hospital of Seattle. This private 189-bed facility in the heart of Seattle is looking for a dynamic physician to serve as an Emergency Physician and Coordinator of our Emergency Department and Prompt Care Center. This hospital, while providing general surgical and medical care, is focusing on specialized services such as in- and outpatient psychiatric program, an inpatient advance eatings disorders treatment program, extensive laser treatment service, a comprehensive program on older adult care services on both an inpatient and outpatient basis, emergency department services and prompt care center. We are looking for a physician with strong leadership capabilities, planning and healthcare system expertise and recent emergency medicine experience. Family practice board eligibility or certification preferred. Please submit your résumé to: Ronald C. M. Bergstrom, Administrator, Saint Cabrini Hospital, Terry & Madison, Seattle, WA 98104.

RADIATION ONCOLOGIST—BC/BE to be Director for newly established radiation treatment center in a private practice setting. Excellent terms with guarantee and incentive plan. Submit CV to: Alfred G. Robinson, MD, 867 W. Lancaster Blvd., Lancaster, CA 93534; (805) 948-5928.

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OREGON OPPORTUNITY—Portland group looking for two new partners. Solid growing practice. First year guarantee plus benefits. Contact: The Friedrich Group, Inc., 9284 Ferncliff NE, Bainbridge Island, WA 98110; (206) 842-5248.

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FAMILY PRACTITIONER for small active medical group of five Internists/specialists in Southern California, west Riverside County; 30 minutes from Orange County. Competitive salary with bonus plan. Malpractice insurance paid. Position available August '86. Send CV to Number 139, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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August 14-15—**Otolaryngology Maxillofacial Trauma.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

August 21-22—**Surviving the Elements.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

September 18-22—**Washington State Medical Association Annual Meeting.** Spokane. Thursday-Monday. Contact: WSMA, 900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 623-4801.

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CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 623-4801.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: 1987: Date and place to be announced.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 863-5522. Annual Meeting: March 6-11, 1987, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 18-20, 1986, Snowmass.

Hawaii Medical Association—320 Ward Ave, Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1986, Westin Ilikai Hotel, Honolulu.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 23-26, 1986, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 2-4, 1986, Holiday Inn, Bozeman.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1987: Date and place to be announced.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: 1987: Date and place to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): 1987: Date and place to be announced.

Utah State Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 10-12, 1986, Yarrow Holiday Inn, Park City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 623-4801. Annual Meeting: September 18-22, 1986, Spokane.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1987: Date and place to be announced.

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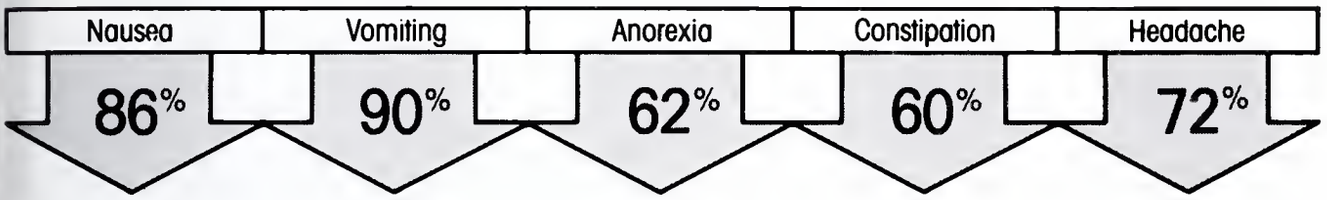

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References: 1. Data on file, Hoffmann-La Roche Inc., Nutley, NJ 2. Feighner JP, *et al. Psychopharmacology 61*:217-225, Mar 22, 1979

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Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

***Usage in Pregnancy*: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

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Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady state concentrations of the tricyclic drugs. Concomitant use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

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Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

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How Supplied: *Double strength (DS) Tablets*, white, film-coated, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt), and *Tablets*, blue, film-coated, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt). Available in bottles of 100 and 500, Tel-E-Dose® packages of 100, Prescription Paks of 50.

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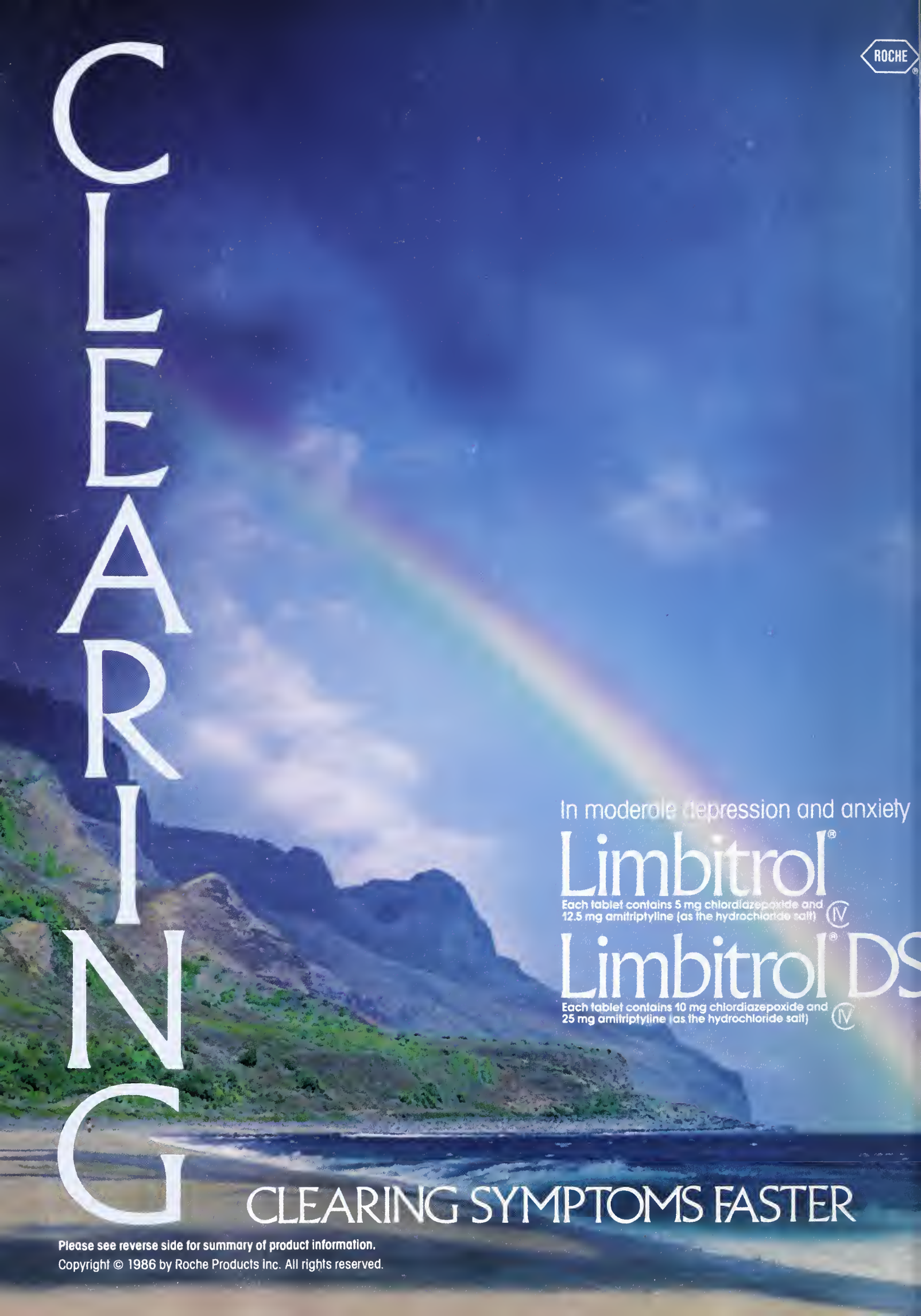

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The Western Journal of Medicine

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before Otoscopic view of tympanic membrane in a patient who did not respond to ampicillin

after Same patient after ten days of Bactrim (trimethoprim and sulfamethoxazole/Roche) therapy

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Simple to take.

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in acute otitis media

- **Penetrates and clears middle-ear fluid of susceptible strains of *H. influenzae* and *S. pneumoniae*[1]**
- **Reduces evidence of inflammation and bulging eardrum[2]**
- **Results in a reduction of fever, pain and other symptoms[2,3]**

Active against 86% of *H. influenzae in vitro*—even amoxicillin- and ampicillin-resistant strains

Overall, 86% of *Haemophilus influenzae* strains taken from sputum cultures prove susceptible *in vitro* to Bactrim.[4] In one study, 100% of 191 ampicillin-resistant *H. influenzae* isolates were susceptible to Bactrim.[5] However, *in vitro* data do not necessarily correlate with clinical results.

Active against 91% of *S. pneumoniae in vitro*

In sputum cultures of *Streptococcus pneumoniae,* the most frequent pathogen in acute otitis media, 91% of isolates show susceptibility *in vitro* to Bactrim.[4]

Excellent clinical activity—and economical

In comparative clinical trials in children with acute otitis media, Bactrim *b.i.d.* was unsurpassed by ampicillin, amoxicillin or cefaclor.[6]
And the average cost of Bactrim is lower than that of cefaclor and comparable to that of ampicillin and amoxicillin.[7]
Bactrim is indicated in acute otitis media due to susceptible organisms when it offers an advantage over other antimicrobials. Bactrim is contraindicated in pregnancy, lactation, infants under two months of age and documented megaloblastic anemia due to folate deficiency. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age.

Cherry-flavored suspension

Bactrim™ Pediatric

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References: 1. Klimek JJ *et al: J Pediatr 96:*1087-1089, Jun 1980. 2. Schwartz RH *et al: Rev Infect Dis 4:*514-516, Mar-Apr 1982. 3. Cooper J, Inman JS, Dawson AF: *Practitioner 217:*804-809, Nov 1976. 4. Antibiotic Sensitivity Report, Winter 1983. BAC-DATA Medical Information Systems, Inc. 5. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 6. Wormser GP, Keusch GT, Heel RC: *Drugs 24:*459-518, Dec 1982. 7. *Med Lett Drugs Ther 23:*93-95, Oct 30, 1981.

Please see summary of product information on the following page.

References: 1. Klimek JJ *et al: J Pediatr* 96:1087-1089, Jun 1980. 2. Schwartz RH *et al: Rev Infect Dis* 4:514-516, Mar-Apr 1982. 3. Cooper J, Inman JS, Dawson AF: *Practitioner* 217:804-809, Nov 1976. 4. Antibiotic Sensitivity Report, Winter 1983. BAC-DATA Medical Information Systems, Inc. 5. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 6. Wormser GP, Keusch GT, Heel RC: *Drugs* 24:459-518, Dec 1982. 7. *Med Lett Drugs Ther* 23:93-95, Oct 30, 1981.

BACTRIM™ (trimethoprim and sulfamethoxazole/Roche)

Before prescribing, please consult complete product information, a summary of which follows:
Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii*. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination. *Note:* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.
For acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over other antimicrobials. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.
For acute exacerbations of chronic bronchitis in adults due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over a single antimicrobial agent.
For enteritis due to susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.
Also for the treatment of documented *Pneumocystis carinii* pneumonitis.
Contraindications: Hypersensitivity to trimethoprim or sulfonamides; patients with documented megaloblastic anemia due to folate deficiency; pregnancy at term; nursing mothers because sulfonamides are excreted in human milk and may cause kernicterus; infants less than 2 months of age.
Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, hepatocellular necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.
Precautions: *General:* Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients.
Pregnancy: Teratogenic Effects: Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus.
Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, hepatocellular necrosis, diarrhea, pseudomembranous colitis and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.
Dosage: Not recommended for infants less than two months of age.
URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN:
Adults: Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days. Use identical daily dosage for 5 days for shigellosis
Children: Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. Use identical daily dosage for 5 days for shigellosis.
For patients with renal impairment: Use recommended dosage regimen when creatinine clearance is above 30 ml/min. If creatinine clearance is between 15 and 30 ml/min, use one-half the usual regimen. Bactrim is not recommended if creatinine clearance is below 15 ml/min.
ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS:
Usual adult dosage: 1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 14 days.
PNEUMOCYSTIS CARINII PNEUMONITIS:
Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.
Supplied: *Double Strength (DS) tablets*, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100, 250 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 20. *Tablets*, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40. *Pediatric Suspension*, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); cherry flavored—bottles of 100 ml and 16 oz (1 pint). *Suspension*, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); fruit-licorice flavored—bottles of 16 oz (1 pint).

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(nadolol tablets)

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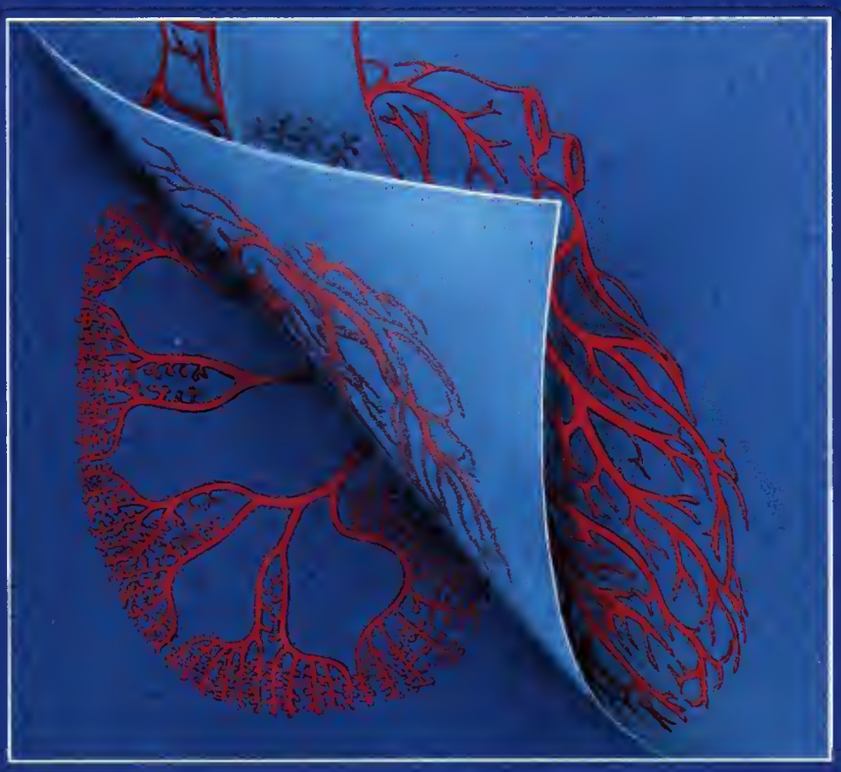
AN UNDERLYING PHARMACOLOGIC CONSIDERATION



By preserving renal blood flow, CORGARD can minimize the compensatory sodium and water retention which may aggravate hypertension.

In a 2-year study of 106 hypertensive patients treated with CORGARD, serum creatinine, an indicator of renal function, decreased 20% from baseline.[1]

CORGARD®
(nadolol tablets)
Preserves renal blood flow

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...e brief summary of prescribing information on adjacent page.

CORGARD®
(nadolol tablets)
Preserves renal blood flow

CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: CORGARD (nadolol) is a synthetic non-selective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2- week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect; monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 years oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy Category C—In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE—For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg q.d. (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg q.d. (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and in Unimatic® unit-dose packs of 100 tablets. The 40 mg, 80 mg, and 120 mg potencies are also available in bottles of 1000 tablets. (J3-527E)

References: 1. Alexander JC, Christie MH, Vernam KA, et al: Long-term experience with nadolol in treatment of hypertension and angina pectoris. Am Heart J 108:1136-1140, 1984.

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From the San Francisco Bay Area Regional Poison Control Center; the Medical Service, Schools of Medicine and Pharmacy, University of California, San Francisco; the Department of Surgery, University of California, Davis, School of Medicine, and Brookside Hospital, San Pablo, California. Dr Pond is now affiliated with Princess Alexandra Hospital, Brisbane, Australia.

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"With [CAPOTEN® (captopril tablets)] it appears that for the first time ever a patient can feel as well on treatment for high blood pressure as he does off it."[1]

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†**CAPOTEN may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. See INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.**

‡The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.

Reference:

1. Stumpe KO, Overlack A, Kolloch R, et al: Long-term efficacy of angiotensin-converting-enzyme inhibition with captopril in mild-to-moderate essential hypertension. Br J Clin Pharmacol 14(suppl 2):121S-126S, 1982.

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INDICATIONS: Hypertension—CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Neutropenia/Agranulocytosis—Neutropenia ($<1000/mm^3$) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine <1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count $<1000/mm^3$) withdraw captopril and closely follow the patient's course.

Proteinuria—Total urinary proteins >1 g/day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy, patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function,* Hypertension—Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction.

Surgery/Anesthesia—If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity—In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis—Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C—There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal—About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis have occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic—Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension may occur, see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—About 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

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MARK C. HOUSTON, MD
Dr Houston is Assistant Professor of Medicine; Co-Director, Medical Intensive Care Unit, and Medical Director, Cooperative Care Center, Vanderbilt University School of Medicine and Vanderbilt Medical Center, Nashville, Tennessee.

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From the Division of Pulmonary Medicine, White Memorial Medical Center, Los Angeles, and Pulmonary Division, Wadsworth Veterans Administration Medical Center, Los Angeles.

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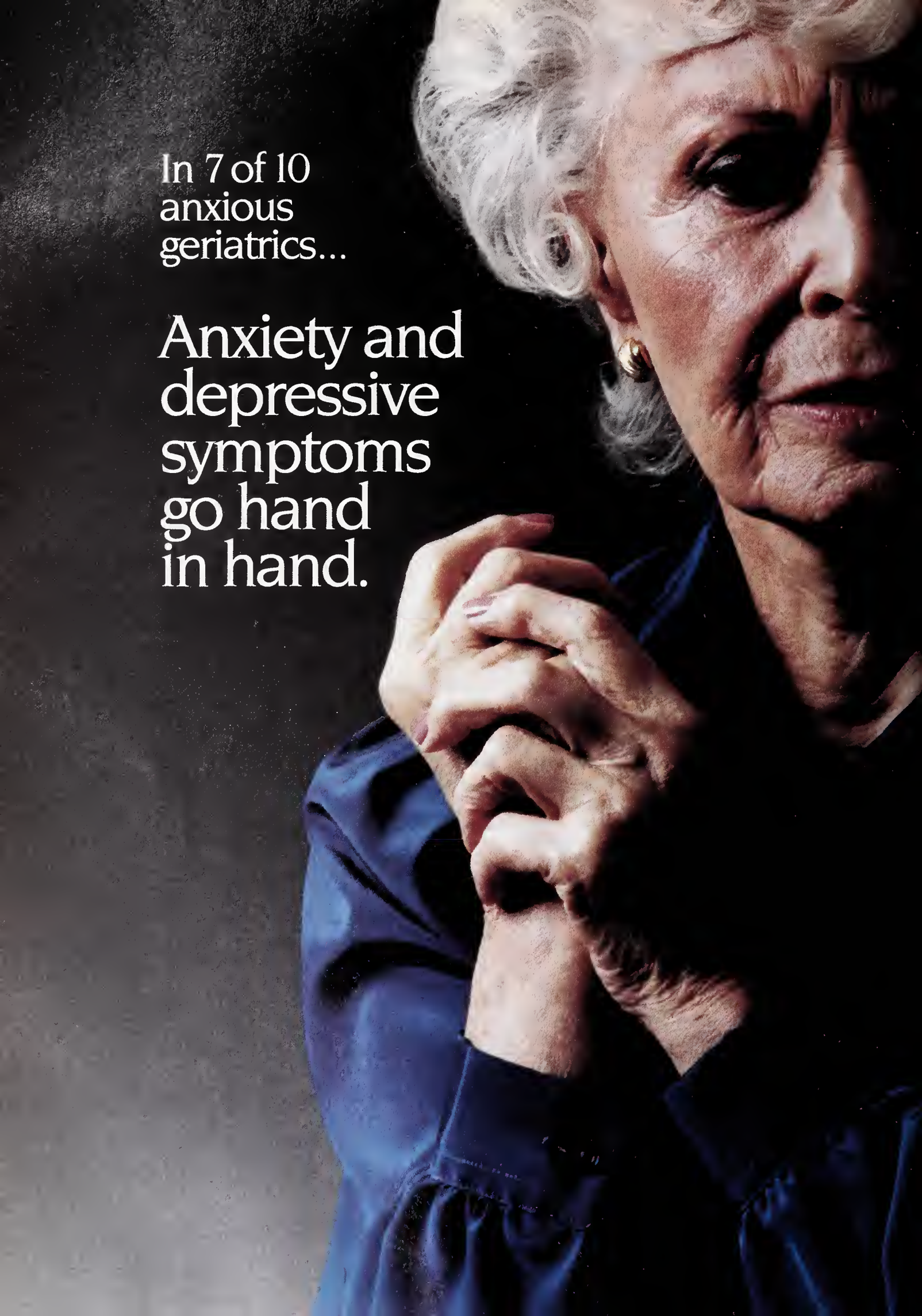
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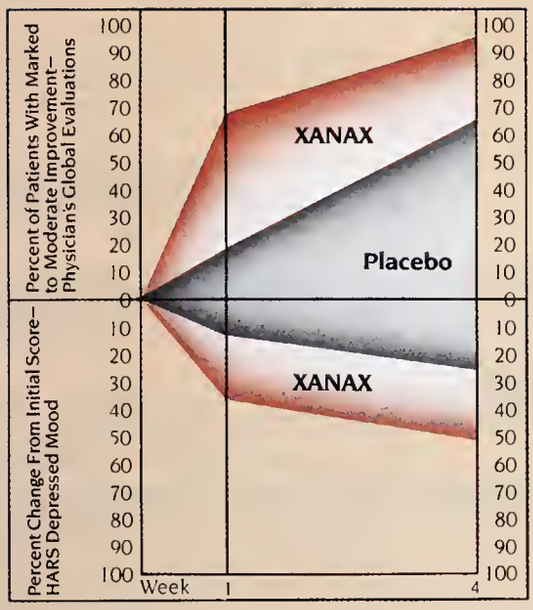

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- Well tolerated—side effects, if they occur, are generally observed at the beginning of therapy and usually disappear with continued medication. Drowsiness and light-headedness were the most commonly reported adverse reactions
- Does not cause cardiovascular toxicity
- **Specific geriatric dosage**—0.25 mg, two or three times daily

1 Cohn JB. Double-blind safety and efficacy comparison of alprazolam and placebo in the treatment of anxiety in geriatric patients. *Curr Ther Res* 1984;35(1):100-112

Xanax® 0.25 mg Tablets
alprazolam C IV

Upjohn 100 A Century of Caring 1886·1986

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Kalamazoo, Michigan 49001, USA

Please see adjacent page for brief summary of prescribing information.

XANAX® Tablets
(alprazolam) ©

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, eg, drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes of unknown significance have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

B-4-S

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January 1986

Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ADVANCES IN UPPER EXTREMITY SURGERY AND REHABILITATION—Edited by John A. Boswick, Jr, MD, Attending Surgeon, Saint Joseph, General Rose and Veterans Hospitals, and Former Professor of Surgery and Chief, Hand Surgical Service, University of Colorado, Denver. Aspen Publishers, Inc, 1600 Research Boulevard, Rockville, MD 20850, 1986. 293 pages, $43.50.

ALLERGY—Edited by Allen P. Kaplan, MD, Professor of Medicine and Head, Division of Allergy, Rheumatology and Clinical Immunology, State University of New York at Stoney Brook, School of Medicine, Stony Brook, New York. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 692 pages, $89.50.

ANESTHETIC MANAGEMENT OF DIFFICULT AND ROUTINE PEDIATRIC PATIENTS—Edited by Frederic A. Berry, MD, Professor of Anesthesiology and Pediatrics, Children's Medical Center of the University of Virginia, Charlottesville, Virginia. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 440 pages, $38.

BRACHIAL PLEXUS INJURIES—Robert D. Leffert, MD, Associate Professor of Orthopaedic Surgery, Harvard Medical School, and Chief of the Surgical Upper Extremity Rehabilitation Unit and of the Department of Rehabilitation Medicine, Massachusetts General Hospital, Boston. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 235 pages, $50.

BURNSIDE'S MEDICAL EXAMINATION REVIEW—Edited by John W. Burnside, MD, Professor of Medicine, Milton S. Hershey Medical Center, Pennsylvania State University College of Medicine, Hershey, Pa. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 797 pages, $49.

CLINICAL ASPECTS OF PERINATAL MEDICINE, Volume II—Manohar Rathi, MD, Chairman, Department of Pediatrics; Director, Perinatal Medicine, Christ Hospital, Oak Lawn, Illinois, and Associate Professor of Pediatrics, Rush Medical College, Chicago. MacMillan Publishing Company, 866 Third Avenue, New York, NY 10022, 1986. 216 pages, $34.95.

CLINICAL COMPUTED TOMOGRAPHY: ILLUSTRATED PROCEDURAL GUIDE—Lee C. Chiu, MD, Professor, Radiological Sciences, UCLA School of Medicine, and Medical Director, Harbor-UCLA Diagnostic Imaging Center, Torrance, Calif; James D. Lipcamon, RTR, Chief Technologist, Harbor-UCLA Diagnostic Imaging Center, Torrance, Calif, and Victoria S. Yiu-Chiu, MD, Ultrasound Division, Long Beach Memorial Medical Center, Long Beach, Calif. Aspen Systems Corporation, 1600 Research Blvd, Rockville, MD 20850, 1986. 261 pages with 298 illustrations, $37.50.

CLINICAL PRACTICE AND COST CONTAINMENT: A PHYSICIAN'S PERSPECTIVE—Henry A. Shenkin, MD, retired neurosurgeon and consultant, Episcopal Hospital, Philadelphia. Praeger Publishers, 521 Fifth Ave, New York, NY 10175, 1986. 137 pages, $39.95.

DISEASE PREVENTION AND HEALTH PROMOTION—A Handbook for Physicians—Edited by John Holbrook, MD, Associate Professor, Internal Medicine, University of Utah School of Medicine, Salt Lake City. Praeger Publishers, 521 Fifth Avenue, New York, NY 10175, 1986. 254 pages, $39.95.

DRUGS AND RENAL DISEASE, 2ND EDITION—Volume 2 in MONOGRAPHS IN CLINICAL PHARMACOLOGY—William M. Bennett, MD, Professor of Medicine and Pharmacology, and Head, Division of Nephrology; Thomas A. Golper, MD, Associate Professor of Medicine, Division of Nephrology, and Director of Clinical Nephrology, Adult Continuous Ambulatory Peritoneal Dialysis and Extracorporeal Services; David A. McCarron, MD, Associate Professor of Medicine, Division of Nephrology/Hypertension, and Director of the Hypertension Program, and George A. Porter, MD, Professor and Chairman, Department of Medicine, The Oregon Health Sciences University, Portland, and Judith A. Whitworth, MD, PhD, Assistant Director, Department of Nephrology, The Royal Melbourne Hospital, and Senior Associate, Department of Medicine, and Research Associate, Howard Florey Institute of Experimental Physiology and Medicine, University of Melbourne, Victoria, Australia. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 198 pages, $25.

ENDOUROLOGY—Edited by Culley C. Carson, MD, Associate Professor of Urology, and N. Reed Dunnick, MD, Professor of Radiology, and Chief, Sections of Uroradiology and Vascular/Interventional Radiology, Duke University Medical Center, Durham, North Carolina. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 315 pages, $58.

ORGANIZED BIBLIOGRAPHY OF THE MICROSURGICAL LITERATURE—Donald L. Ballantyne, PhD, Professor of Experimental Surgery, Director of Microsurgical Research and Training Laboratories, Institute of Reconstructive Plastic Surgery, New York University Medical Center, and Benjamin B. Rosenberg, MD, Shaare Zedek Medical Center, Jerusalem, with a contribution by Lloyd Hoffman, MD, and Court Cutting, MD, Institute of Reconstructive Plastic Surgery, New York University Medical Center. Aspen Systems Corporation, 1600 Research Blvd, Rockville, MD 20840, 1985. 386 pages, softbound, price not listed.

OTOLOGIC RADIOLOGY, WITH CLINICAL CORRELATIONS—Ramon Ruenes, MD, Professor of Radiology, National Autonomous University of Mexico, and Director, Center for Head and Neck Radiology, Mexico City, and Antonio De la Cruz, MD, Director of Education, House Ear Institute, and Associate Clinical Professor of Otolaryngology, University of Southern California School of Medicine, Los Angeles. Macmillan Publishing Company, 866 Third Ave, New York, NY 10022, 1986. 183 pages, $49.95.

STATE OF THE ART REVIEWS IN OCCUPATIONAL MEDICINE—The Microelectronics Industry: January-March 1986, Vol 1, No 1—Guest Editor: Joseph LaDou, MD, Acting Chief, Division of Occupational and Environmental Medicine, University of California, San Francisco. Hanley & Belfus, Inc, 210 South 13th St, Philadelphia, PA 19107, 1986. 197 pages, single copies $22. The subscription price is $48 per year (US), $56 outside US (add $12 for surface, $20 for air mail).

A SYSTEM OF SCIENTIFIC MEDICINE—Philanthropic Foundations in the Flexner Era—Howard Berliner, Associate Research Scientist, Conservation of Human Resources, Columbia University. Published in 1985 by Tavistock Publications in association with Methuen, Inc, 29 West 35th St, New York, NY 10001, and Tavistock Publications Ltd, II New Fetter Lane, London EC4P 4EE. 190 pages, $29.95 (cloth); $12.95 (paperback).

ow on MEDI-CAL formulary

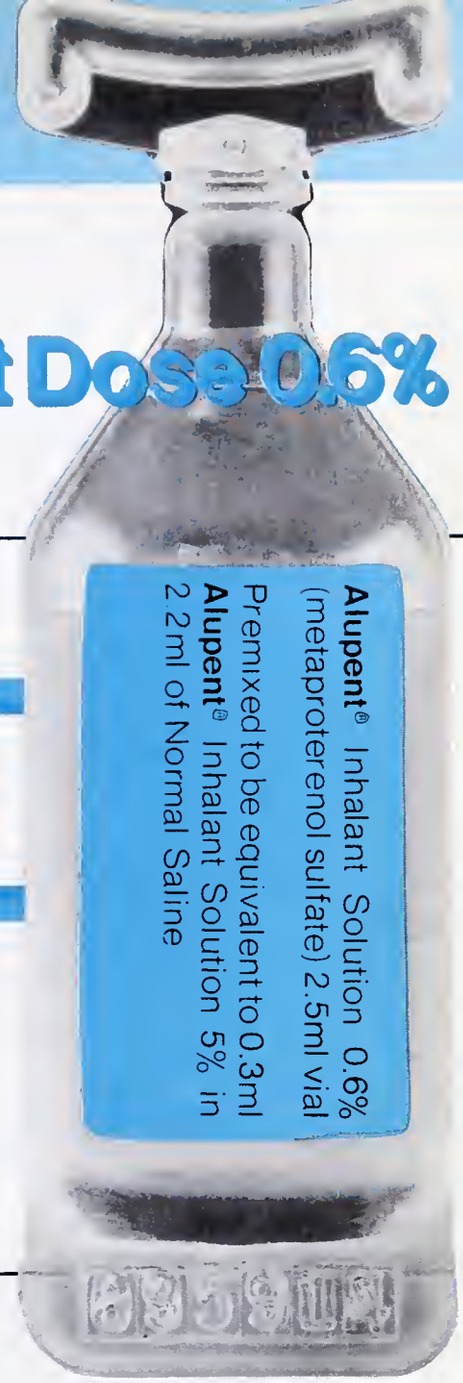
Alupent® Solution Unit Dose 0.6%

metaproterenol sulfate)

bronchodilator

Medi-Cal Number : **1031F-CC**

- Up to six hours of bronchodilator efficacy
- Accuracy and convenience in a single vial
- No metabisulfites



lpent®
taproterenol sulfate)

Inhalant Solution
Unit-Dose Vial
Bronchodilator

f Summary of Prescribing Information

ICATIONS AND USAGE Alupent® (metaproterenol sulfate) Inhalant ution is indicated as bronchodilator for bronchial asthma and for ersible bronchospasm which may occur in association with bronchitis emphysema

NTRAINDICATIONS Use in patients with cardiac arrhythmias asso- ed with tachycardia is contraindicated

ough rare, immediate hypersensitivity reactions can occur Therefore. pent (metaproterenol sulfate) Inhalant Solution, 0 6% is contraindicated atients with a history of hypersensitivity to any of its components

RNINGS Excessive use of adrenergic aerosols is potentially dan- ous Fatalities have been reported following excessive use of Alupent etaproterenol sulfate) as with other sympathomimetic inhalation parations, and the exact cause is unknown Cardiac arrest was noted everal cases.

adoxical bronchoconstriction with repeated excessive administration been noted with sympathomimetic agents.

ients should be advised to contact their physician in the event that they not respond to their usual dose of sympathomimetic amine aerosol

ECAUTIONS Because Alupent (metaproterenol sulfate) Inhalant Solu- n is a sympathomimetic drug, it should be used with great caution in ients with hypertension, coronary artery disease, congestive heart ure, hyperthyroidism or diabetes, or when there is sensitivity to sympa- mimetic amines.

ormation for Patients Extreme care must be exercised with respect to administration of additional sympathomimetic agents. A sufficient erval of time should elapse prior to administration of another sympatho- metic agent.

rcinogenesis Long-term studies in mice and rats to evaluate the oral rcinogenic potential of metaproterenol sulfate have not been completed udies of metaproterenol sulfate have not been conducted to determine utagenic potential or effect on fertility

egnancy *Teratogenic Effects: Pregnancy Category C* Alupent (meta- proterenol sulfate) has been shown to be teratogenic and embryocidal in rabbits when given orally in doses 620 times the human inhalation dose. There are no adequate and well-controlled studies in pregnant women. Alupent should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Oral reproduction studies in mice, rats and rabbits showed no teratogenic or embryocidal effects at 50 mg/kg corresponding to 310 times the human inhalation dose. Teratogenic effects in the rabbit included skeletal abnormalities and hydrocephalus with bone separation.

Nursing Mothers It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Alupent (metaproterenol sulfate) is administered to a nursing woman

Pediatric Use Safety and effectiveness in children below the age of 12 have not been established

ADVERSE REACTIONS Adverse reactions are similar to those noted with other sympathomimetic agents

The most frequent adverse reactions to Alupent (metaproterenol sulfate) are nervousness and tachycardia which occur in about 1 in 7 patients, tremor which occurs in about 1 to 20 patients and nausea which occurs in about 1 in 50 patients Less frequent adverse reactions are hypertension, palpitations, vomiting and bad taste which occur in approximately 1 in 300 patients.

HOW SUPPLIED Alupent (metaproterenol sulfate) Inhalant Solution Unit Dose Vials are supplied as 0.6% clear colorless or nearly colorless solution, each vial containing 2.5 ml, with 25 vials per box Do not use the solution if it is brown or has a precipitate.

Consult package insert before prescribing AL-UD-BPI-5/86

Boehringer Ingelheim

Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877

AL-3642

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★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

OR HYPERTENSIVE PATIENTS INTOLERANT OF BETA-BLOCKER THERAPY

CONSIDER

VASOTEC®

(ENALAPRIL MALEATE | MSD)

For a Brief Summary of Prescribing Information,
please see last page of this advertisement.

FOR APPROPRIATE PATIENTS WITH MILD TO MODERATE HYPERTEN

IT MAY CHANGE THE WA YOUR PATIENTS FEEL O

VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product.

NTIHYPERTENSIVE THERAPY

- Certain subjective symptoms such as malaise and drowsiness, which may interfere with physical or mental activity, have not been characteristic of VASOTEC. This may be related to the specificity of action of VASOTEC on the renin-angiotensin-aldosterone system.

- In worldwide controlled clinical trials, VASOTEC was generally well tolerated. The overall percentage of patients reporting adverse effects was comparable to placebo.

- For the most part, adverse effects in clinical trials were mild and transient and usually did not require discontinuation of therapy.

Angioedema has been reported in patients treated with angiotensin-converting-enzyme inhibitors, including VASOTEC (0.2% of patients treated with VASOTEC). Angioedema associated with laryngeal edema and/or shock may be fatal. **If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately** (see ADVERSE REACTIONS).

Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. Therefore, discontinue therapy with a beta blocker only in accordance with the recommendations in the prescribing information for that product. Begin therapy with VASOTEC on the day following the last day of therapy with the beta blocker.

FOR MANY HYPERTENSIVE PATIENTS

ONCE-A-DAY

VASOTEC®

(ENALAPRIL MALEATE | MSD)

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For a Brief Summary of Prescribing Information, please see next page of this advertisement.

FOR MANY HYPERTENSIVE PATIENTS

ONCE-A-DAY

VASOTEC®

(ENALAPRIL MALEATE | MSD)

Contraindications: VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product

Warnings: *Angioedema.* Angioedema has been reported in patients treated with angiotensin-converting-enzyme inhibitors, including VASOTEC. Angioedema associated with laryngeal edema and/or shock may be fatal. **If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased.

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Neutropenia/Agranulocytosis: Another angiotensin-converting-enzyme inhibitor has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General: Impaired Renal Function:* In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of VASOTEC and/or discontinuation of the diuretic may be required.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia. (See *Drug Interactions.*)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, tongue, difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Neutropenia Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC® (Enalapril Maleate, MSD) is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents. VASOTEC has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC may attenuate potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril, but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

There are no adequate and well-controlled studies in pregnant women. VASOTEC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2677 patients.

The most frequent clinical adverse experiences in controlled trials were: headache (4.8%), dizziness (4.6%), and fatigue (2.8%). For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences was not related to total daily dosage within the range of 10 to 40 mg. The overall percentage of patients treated with VASOTEC reporting adverse experiences was comparable to placebo.

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.6%), rash (1.5%), hypotension (1.4%), cough (1.3%), nausea (1.3%), and orthostatic effects (1.3%).

Clinical adverse experiences occurring in 0.5% to 1.0% of patients in the controlled trials included:

Cardiovascular: Syncope, orthostatic hypotension, palpitations, chest pain.

Nervous System: Insomnia, nervousness, paresthesia, somnolence.

Gastrointestinal System: Abdominal pain, vomiting, dyspepsia.

Other: Dyspnea, muscle cramps, hyperhydrosis, impotence, pruritus, asthenia.

Angioedema Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema and/or shock may be fatal. If angioedema of the face, tongue, or glottis occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: Combining the results of clinical trials in patients with hypertension or congestive heart failure, hypotension (including postural hypotension and other orthostatic effects) was reported in 2.3% of patients following the initial dose of enalapril or during extended therapy. In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. (See WARNINGS.)

Clinical Laboratory Test Findings:

Hyperkalemia: (See PRECAUTIONS.)

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.)

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in hypertensive patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

In overseas marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

For more detailed information, consult your MSD representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

J6VS11(003)

MSD
MERCK SHARP & DOHME

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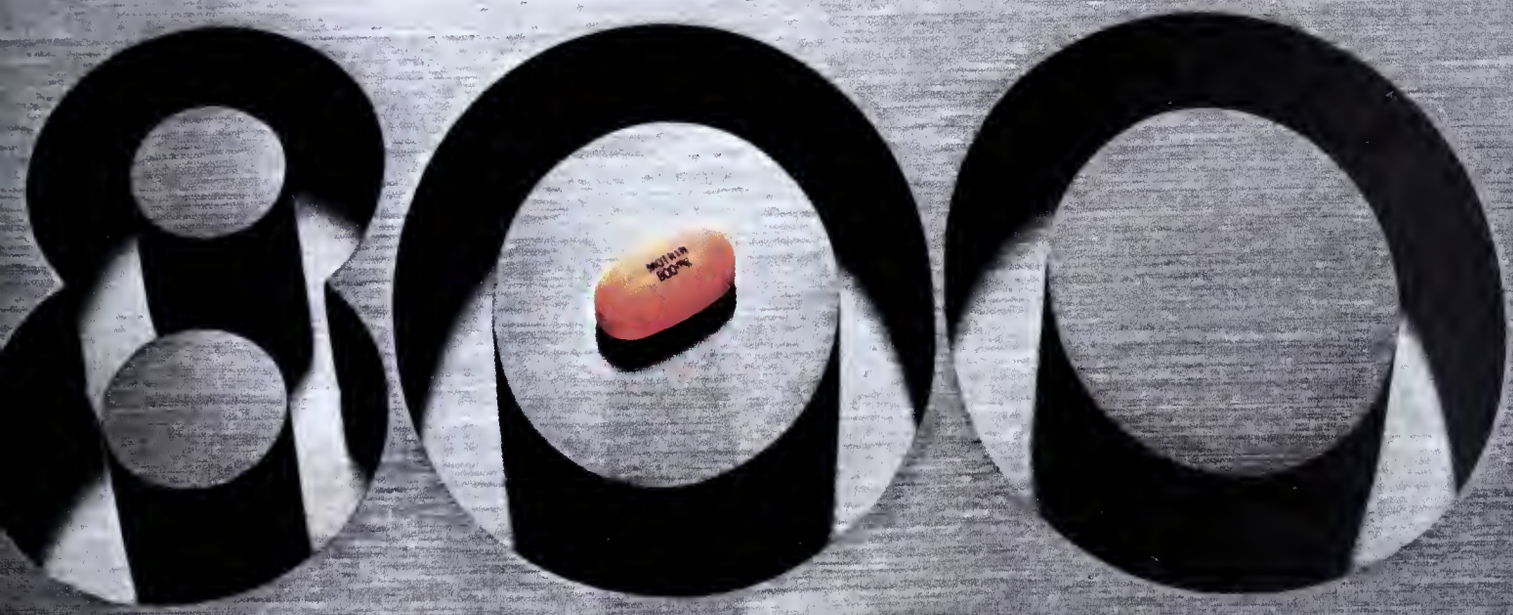

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J-6138 January 1986

Continuing Medical Education

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

October 31-November 2—**Sixth Annual Southwestern Poison and Drug Information Symposium.** Scottsdale Sheraton Resort, Scottsdale. Friday-Sunday. Contact: U of A.

Novemer 14-16—**Fifteenth Annual Radiology Seminar.** Marriott's Camelback Inn, Scottsdale. Friday-Sunday. Contact: Alex Newman, MD, Maricopa Medical Center, (602) 267-5361.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6173.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

September 20—**New Directions in the Treatment of Asthma.** Los Angeles Society of Allergy and Clinical Immunology at Beverly Wilshire Hotel, Beverly Hills. Saturday. Contact: Mrs Geri Coldewey, LASACI, 1626 N Wilcox, #557, Hollywood 90028.

September 26-27—**Allergy Update.** STAN at STAN. Friday-Saturday. Contact: STAN.

October 7-10—**Rheumatology and Clinical Immunology: A Practical Approach.** UCSF at Stanford Court Hotel, San Francisco. Tuesday-Friday. Contact: UCSF.

October 27-31—**The Western Society of Allergy and Immunology's 25th Annual Session.** Marriott Hotel, Maui, Hawaii. Monday-Friday. Contact: Joyce Gullixson, 1700 SW Columbia, Portland, OR 97201. (503) 224-6159.

December 21-27—**Allergy, Immunology and the Practicing Physician—"Christmas '86—Maui."** Hawaii Medical Association at Royal Lahaina Resort, Kaanapali Beach, Maui. One week. 18 hrs. Fee: $385. Contact: Joe Harrison, MD, Symposium Maui, Inc, PO Box 10185, Lahaina, HI 96761. (808) 879-8182 or 661-8032.

(Continued on Page 168)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

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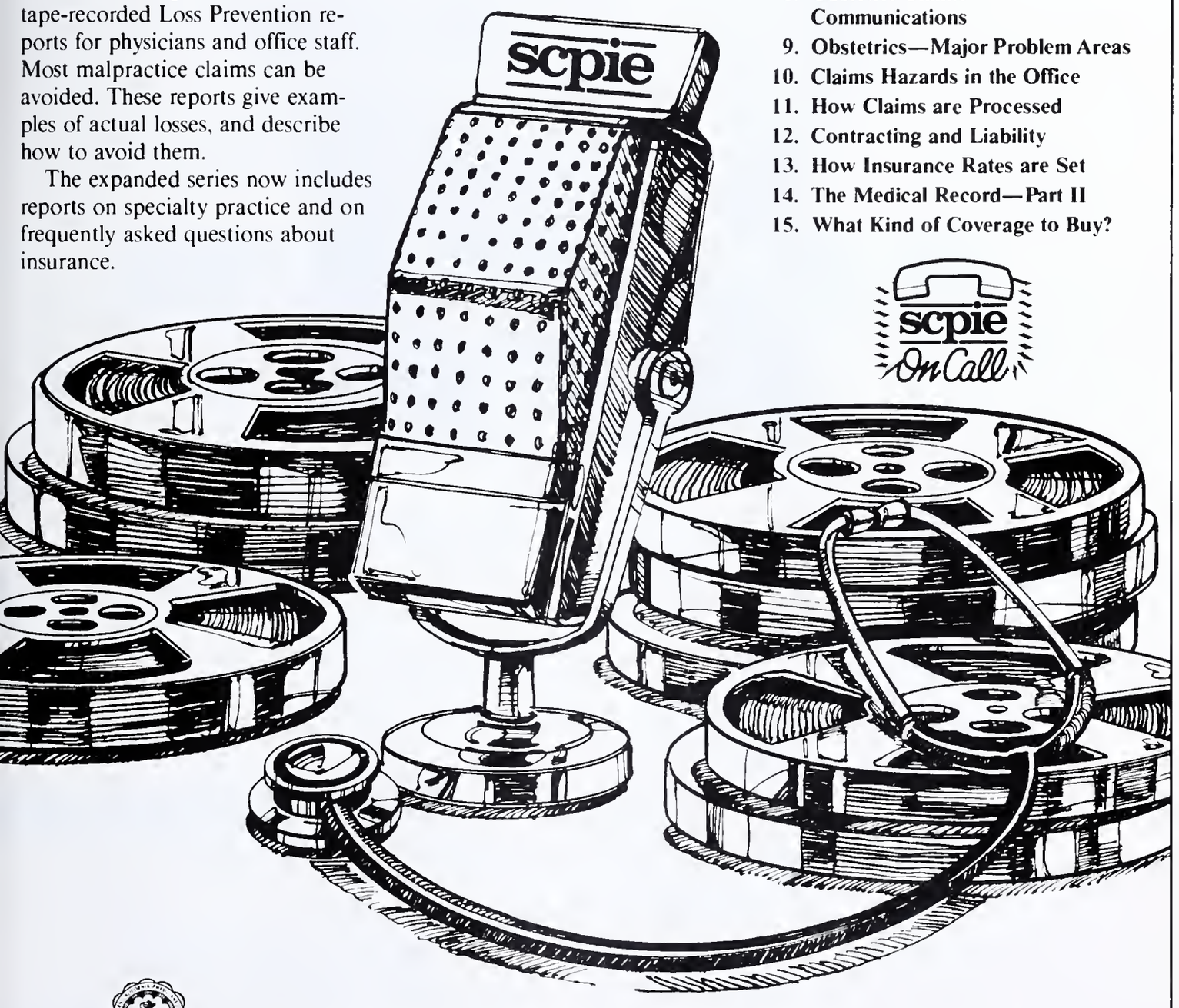

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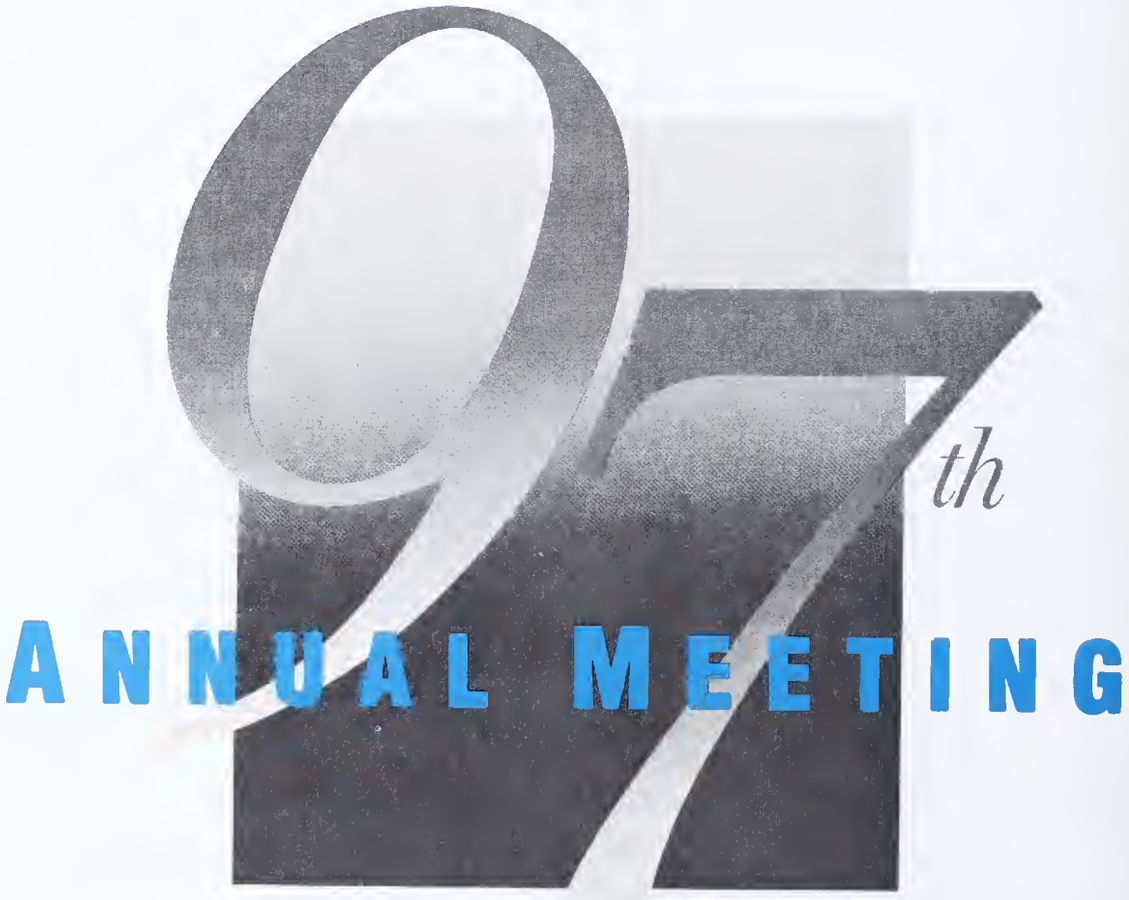

September 18-21, 1986

Inn at the Park
Spokane, Washington

Registration Form

Washington State Medical Association
97th Annual Meeting, September 18-21, 1986
Inn at the Park, Spokane, Washington

Return this form to:
Washington State Medical Association
2033 Sixth Avenue, #900
Seattle, WA 98121

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☐ WSMA Auxiliary Meeting—Registration Fee—$10	$_____
☐ Resident/Medical Student—No Charge	N/C

Social Events/Activities

	Cost Before Sept. 1	Cost After Sept. 1	Amount
Friday, September 19			
Annual Banquet—Presidents' Dinner	$20	$23	$_____
American College of Physicians/Washington State Society of Internal Medicine Luncheon	$10	$12	$_____
Saturday, September 20			
Christian Medical Society Breakfast	$ 9	$10	$_____
Washington State Psychiatric Association Luncheon	$ 9	$11	$_____
WAFP Risk Management Luncheon	$12	$14	$_____
WAMPAC Luncheon	**WAMPAC Member** $11	**WAMPAC Member** $13	$_____
	WAMPAC Non-Mbr $16	**WAMPAC Non-Mbr** $18	$_____

For more information about the Fun Run, Tennis or Golf Tournaments, contact:

Jan Monaco, Executive Director
Spokane County Medical Society
W. 1101 College, #370
Spokane, WA 99201
(509) 328-3952

Total Amount Enclosed $_____

WSMA

(Continued from Page 164)

ANESTHESIOLOGY

August 17-22—**Clinical Anesthesia.** California Society of Anesthesiologists at The Waiohai Hotel, Poipu Beach, Kauai. Sunday-Friday. 20 hrs. Contact: Linda P. Londerville, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

September 6-7—**Case Conference.** California Society of Anesthesiologists and Travenol Laboratories at High Sierra Hotel, Lake Tahoe. Saturday-Sunday. 9 hrs. Contact: Linda P. Londerville, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

September 26-28—**Anesthesia Practice 1986.** Anesthesiology Educational Foundation at Monterey. Friday-Sunday. 10.5 hrs. Contact: Anesthesiology Educational Foundation, PO Box 24230, Federal Bldg, Los Angeles 90024.

October 22-28—**Post-ASA Annual Meeting.** California Society of Anesthesiologists at Maui Inter-Continental Hotel, Hawaii. Wednesday-Tuesday. 20 hrs. Contact: Linda P. Londerville, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

January 8-11—**Anesthesia Update—1987.** UCSD at Hotel Inter-Continental, San Diego. Thursday-Sunday. 20 hrs. Contact: UCSD.

January 30—February 1—**25th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Marriott Hotel, Los Angeles. Friday-Sunday. 15 hrs. Fee: $175. Contact: Wayne Herbert, MD, Children's Hospital of Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

CANCER

September 25-26—**Advances in Treatment of Leukemia and Marrow Stem Cell Disorders.** UCSF at Fisherman's Wharf Sheraton Hotel, San Francisco. Thursday-Friday. 9 hrs. Fee: $100. Contact: UCSF.

October 27-29—**10th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Island Hotel East, San Diego. Monday-Wednesday. 22 hrs. Fee: $350. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy, San Diego 92121. (619) 453-6222.

December 5-6—**Recent Advances in Occupational Cancer.** UCSF at Cathedral Hill Hotel, San Francisco. Friday-Saturday. Fee: $200. Contact: UCSF.

CARDIOLOGY

September 5-6—**56th Annual Physicians' Postgraduate Symposium on Cardiovascular Disease.** American Heart Association, San Francisco at Cathedral Hill Hotel, San Francisco. Friday-Saturday. 10 hrs. Fee: $100. Contact: Kari Olila, American Heart Association, 421 Powell St, San Francisco 94102. (415) 433-2273.

September 10-11—**54th Annual Fall Symposium and 19th Annual George C. Griffith Scientific Lecture.** American Heart Association, Los Angeles, at Hilton Hotel, Los Angeles. Wednesday-Thursday. Contact: Marianne Joyce, AHA, 3550 Wilshire Blvd, Los Angeles 90010. (213) 385-4231.

September 10-12—**Cardiovascular Pathology.** STAN at STAN. Wednesday-Friday. Contact: STAN.

September 18-20—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Hotel Meridien, San Francisco. Thursday-Saturday. 15 hrs. Fee: $350. Contact: UCSF.

September 22-26—**American College of Chest Physicians 52nd Annual Scientific Assembly.** San Francisco. Monday-Friday. Contact: ACCP, Division of Education, 911 Busse Highway, Park Ridge, IL 60068. (312) 698-2200.

September 25-27—**Myocardial Dysfunction in Ischemic Heart Disease: Medical and Surgical Considerations.** UCSD at Hotel Inter-Continental, San Diego. Thursday-Saturday. 16 hrs. Fee: $350-375. Contact: UCSD.

October 10—**Cardiac Arrhythmias.** UCD at Woodlake Inn, Sacramento. Friday. Contact: UCD.

October 10-11—**Vascular and Pulmonary Diseases: Diagnosis and Management.** Medical Education Resources at Sheraton at Fisherman's Wharf, San Francisco. Friday-Saturday. 11 hrs. Fee: $295. Contact: Medical Education Resources, Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or in Colorado (303) 798-9682.

October 16-18—**10th Annual Cardiology Update—1986.** American College of Cardiology at Quail Lodge, Carmel. Thursday-Saturday. Contact: ACC, 9111 Old George Town Rd, Bethesda, MD 20814. (301) 897-5400, ext 227.

October 24-26—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

October 25—**9th Annual Northridge Hospital Medical Center Heart Symposium.** Center Plaza Hotel, Los Angeles. Saturday. 6 hrs. Fee: $125. Contact: Dept of Medical Education, Northridge Hospital Medical Center, 18300 Roscoe Blvd, Northridge 91328. (213) 885-8500.

November 1—**The Heart and the Brain: Clinical Interrelationships—Office Management of Stress and Emotionally Induced Cardiovascular Disabilities.** UCI at Center for Health Education, Long Beach. Saturday. Contact: UCI.

November 12—**Pulmonary and Intensive Care Medi-**

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cine. LLU at LLU. Wednesday. 5 hrs. Fee: $60. Contact: LLU.

December 12-13—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Americana Canyon Hotel, Palm Springs. Friday-Saturday. 11 hrs. Fee: $295. Contact: Medical Education Resources, Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or in Colorado (303) 798-9682.

December 12-14—**Advances in Heart Disease.** American College of Cardiology at Hyatt Regency on Union Square, San Francisco. Friday-Sunday. Contact: ACC, 9111 Old George Town Rd, Bethesda, MD 20814. (301) 897-5400, ext 227.

January 23-25—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

January 29-31—**Cardiology '87.** Scripps Memorial Hospital, La Jolla at La Jolla Marriott Hotel, San Diego. Thursday-Saturday. 18 hrs. Fee: $275. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 29-31—**Clinical Nuclear Cardiology: Case Review with the Experts.** American College of Cardiology at Annenberg Center, Rancho Mirage. Thursday-Saturday. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400.

DERMATOLOGY

August 20-24—**Advanced Seminars in Dermatology.** UCSF at Hyatt Lake Tahoe. Wednesday-Sunday. Contact: UCSF.

September 21—**1 Day Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Kona Kai Club, San Diego. Sunday. 7 hrs. Fee: $185. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

September 22-28—**Combined Skin Pathology.** UCI at Newporter Inn, Newport Beach. Monday-Sunday. Contact: UCI.

September 28—**1 Day Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Holiday Inn on

Union Square, San Francisco. Sunday. 7 hrs. Fee: $185. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

October 3-4—**15th Annual Mycology Review.** Stanford. Friday-Saturday. Contact: Paul H. Jacobs, MD, Dept of Dermatology, Stanford Medical Center, Stanford 94305. (415) 497-6105.

October 10-12—**6th Postgraduate Course in Medical Mycology (Dermatomycology).** UCSF. Friday-Sunday. 17.5 hrs. Fee: $275. Contact: UCSF.

October 11-12—**The Skin From A to Z.** UCSF. Saturday-Sunday. 10 hrs. Fee: $185. Contact: UCSF.

October 18—**Dermatology.** Kaiser Permanente Medical Group at Ramada Renaissance Hotel, Long Beach. Saturday. 7 hrs. Fee: $100. Contact: Judy Harrison, Dept of Clinical Services, Southern California Permanente Medical Group, 393 E Walnut St, Pasadena 91188. (818) 405-5000.

January 23-25—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** Continuing Medical Education Associates, San Diego. Friday-Sunday. 20 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

EMERGENCY MEDICINE

August 18-22—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD. Monday-Friday. Contact: UCSD.

August 25-29—**Topics in Emergency Medicine.** UCSF at Union Square Holiday Inn, San Francisco. Monday-Friday. 32.5 hrs. Fee: $400. Contact: UCSF.

August 26-29—**Update in Emergency Medicine.** Mercy Medical Center, Redding at Marble Mountain Wilderness (horse-packing). Tuesday-Friday. 10 hrs. Fee: $195. Contact: Shelley Underwood, Inservice Education, PO Box 6009, Redding 96099. (916) 225-6171.

August 30-September 1—**Wilderness Emergency Care.** Mercy Medical Center, Redding at Klamath River (rafting trip). Saturday-Monday. 10 hrs. Fee: $125. Contact: Shelley Underwood, Inservice Education, PO Box 6009, Redding 96099. (916) 225-6171.

September 22-26—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD at Vacation Village Resort, San Diego. Monday-Friday. Contact: UCSD.

October 27-31—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Monday-Friday. 40 hrs. Fee: $550. Contact: UCSF.

October 27-31—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD at Hanalei Hotel, San Diego. Monday-Friday. Contact: UCSD.

November 16—**Emergencies in Medical Practice.** Granada Hills Community Hospital at Sheraton Universal Hotel, North Hollywood. Sunday. 7 hrs. Fee: $100. Contact: Beverly Chaussee, Granada Hills Community Hospital, 10445 Balboa Blvd, Granada Hills 91344. (818) 360-1021, ext 6789.

December 7-13—**Current Concepts in Emergency Care.** American College of Emergency Physicians at Royal Lahaina Resort, Maui. Sunday-Saturday. 25 hrs. Contact: Georgine Elich, Kailani World Travel, 4192 Meridian Ave, Bellingham, WA 98226. USA (800) 426-2561 or in Washington (800) 562-2597.

December 8-12—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD. Monday-Friday. 32 hrs. Fee: $325-440. Contact: UCSD.

January 12-16—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD at San Diego Hilton Hotel. Monday-Friday. 32 hrs. Fee: $325-440. Contact: UCSD.

INTERNAL MEDICINE

August 17-22—**New Advances in Internal Medicine.** UCD at Hyatt Regency, Monterey. Sunday-Friday. Contact: UCD.

August 25-30—**7th Comprehensive Nephrology Review.** UCLA at Miramar Sheraton, Santa Monica. Monday-Saturday. 55.5 hrs. Fee: $695. Contact: UCLA.

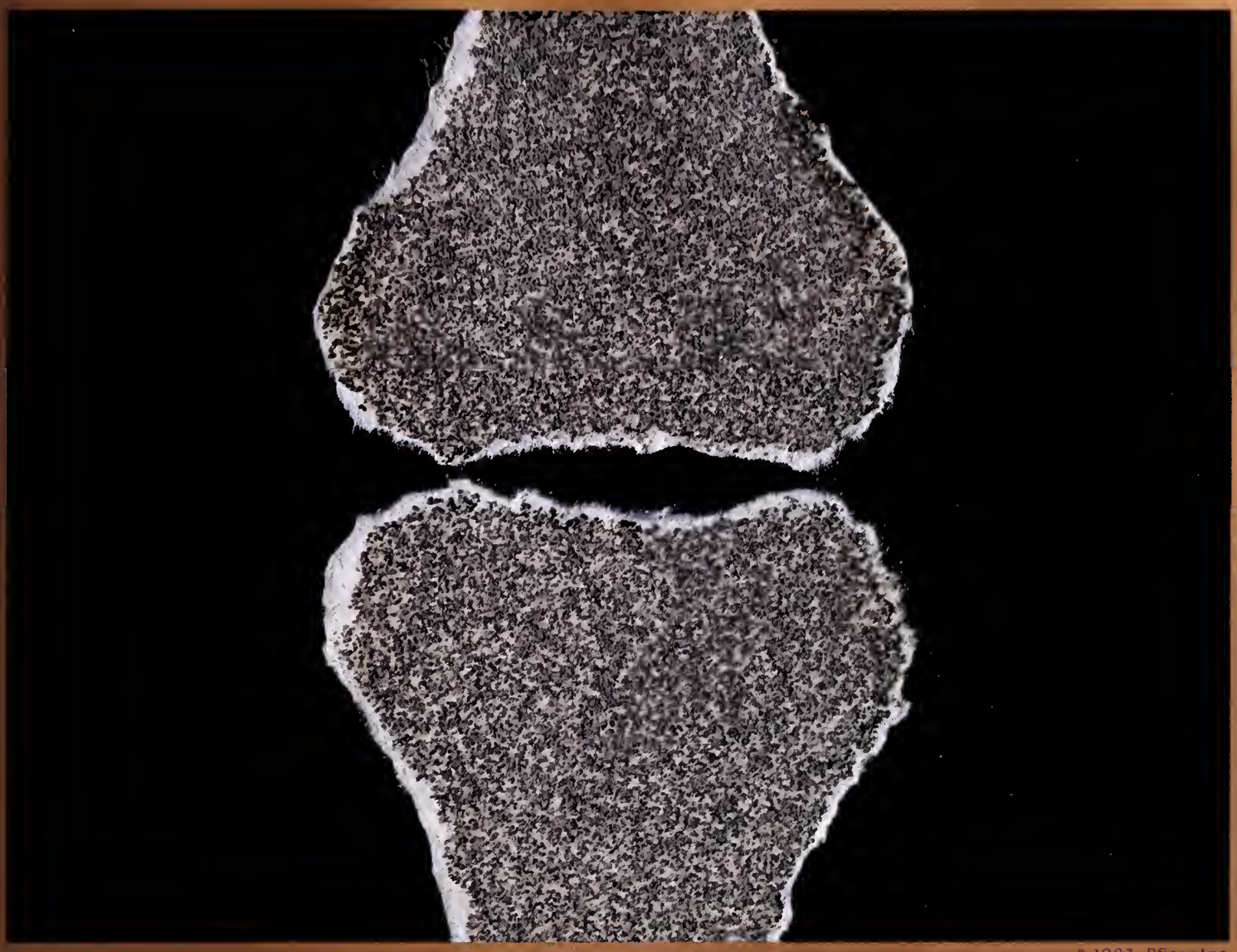
September 8-9—**Parasitic Infections: Advances in the Biology and Clinical Management.** UCSF at St Helena. Monday-Tuesday. 9 hrs. Fee: $65. Contact: Laura Bateson or Mary Fobel, (415) 821-8317 or 476-3049.

September 19-20—**Internal Medicine.** Kaiser Permanente Medical Group at Disneyland Hotel, Anaheim. Friday-Saturday. 11 hrs. Fee: $150. Contact: Judy Harrison, Dept of Clinical Services, Southern California Permanente Medical Group, Pasadena 91188. (818) 405-5000.

October 1—**Angiotensin—Converting Enzyme Inhibitors, New Developments and Current Therapeutic Applications.** Cedars-Sinai Medical Center, Los Angeles. Wednesday. Contact: Lore Kahane, Rm 2049, Cedars-Sinai Medical Center, PO Box 48750, Los Angeles 90048-0750. (213) 855-5547.

October 8—**Gastroenterology—Cholelithiasis and Cholecystitis: New Insights.** LLU at LLU. Wednesday. 4 hrs. Fee: $60. Contact: LLU.

(Continued on Page 173)



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Source: PDR, 1986, Manufacturers' Prescribing Information

Indicates maximum dosage for osteoarthritis and rheumatoid arthritis for the antiarthritic agents shown. Consult manufacturers' prescribing information.

Brief Summary

FELDENE® (piroxicam) Capsules

CONTRAINDICATIONS: FELDENE (piroxicam) should not be used in patients who have previously exhibited hypersensitivity to it, or in individuals with the syndrome comprised of bronchospasm, nasal polyps and angioedema precipitated by aspirin or other nonsteroidal anti-inflammatory drugs

WARNINGS: Peptic ulceration, perforation and G.I. bleeding—sometimes severe, and, in some instances fatal—have been reported with patients receiving FELDENE. If FELDENE must be given to patients with a history of upper gastrointestinal tract disease, the patient should be under close supervision (see ADVERSE REACTIONS).

PRECAUTIONS: Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of piroxicam to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally, nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly.

Because of extensive renal excretion of piroxicam and its biotransformation products (less than 5% of the daily dose excreted unchanged), lower doses of piroxicam should be anticipated in patients with impaired renal function, and they should be carefully monitored.

Although other nonsteroidal anti-inflammatory drugs do not have the same direct effect on platelets that aspirin does, all drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree.

Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop visual complaints during treatment with FELDENE have ophthalmic evaluation.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom abnormal liver tests have occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with FELDENE.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis have been reported with FELDENE. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), FELDENE should be discontinued. (See also ADVERSE REACTIONS.)

Although at the recommended dose of 20 mg/day of FELDENE increased fecal blood loss due to gastrointestinal irritation did not occur, in about 4% of the patients treated with FELDENE alone or concomitantly with aspirin, reductions in hemoglobin and hematocrit values were observed.

Peripheral edema has been observed in approximately 2% of the patients treated with FELDENE. Therefore, FELDENE should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

A combination of dermatological and/or allergic signs and symptoms suggestive of serum sickness have occasionally occurred in conjunction with the use of FELDENE. These include arthralgias, pruritus, fever, fatigue, and rash including vesiculo bullous reactions and exfoliative dermatitis.

DRUG INTERACTIONS: Interactions with coumarin-type anticoagulants have been reported with FELDENE since marketing. Therefore, physicians should closely monitor patients for a change in dosage requirements when administering FELDENE to patients on coumarin-type anticoagulants and other highly protein-bound drugs.

Plasma levels of piroxicam are depressed to approximately 80% of their normal values when FELDENE is administered in conjunction with aspirin (3900 mg/day), but concomitant administration of antacids has no effect on piroxicam plasma levels.

Nonsteroidal anti-inflammatory agents, including FELDENE, have been reported to increase steady state plasma lithium levels. It is recommended that plasma lithium levels be monitored when initiating, adjusting and discontinuing FELDENE.

Carcinogenesis, Chronic Animal Toxicity and Impairment of Fertility: Subacute and chronic toxicity studies have been carried out in rats, mice, dogs, and monkeys.

The pathology most often seen was that characteristically associated with the animal toxicology of anti-inflammatory agents: renal papillary necrosis (see PRECAUTIONS) and gastrointestinal lesions.

In classical studies in laboratory animals, piroxicam did not show any teratogenic potential.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy and Nursing Mothers: Like other drugs which inhibit the synthesis and release of prostaglandins, piroxicam administration continued late into pregnancy increased the incidence of dystocia and delayed parturition in animals. Gastrointestinal tract toxicity was increased in pregnant females in the last trimester of pregnancy compared to non-pregnant females or females in earlier trimesters of pregnancy.

FELDENE is not recommended for use in nursing mothers or in pregnant women because of the animal findings and since safety for such use has not been established in humans.

Use In Children: Dosage recommendations and indications for use in children have not been established.

ADVERSE REACTIONS: Gastrointestinal symptoms are the most prominent side effects, occurring in approximately 20% of the patients, which in most instances did not interfere with the course of therapy. Of the patients experiencing gastrointestinal side effects, approximately 5% discontinued therapy with an overall incidence of peptic ulceration of about 1%.

Adverse reactions are listed below by body system for all patients in clinical trials with FELDENE (piroxicam) at doses of 20 mg/day.

Incidence Greater Than 1%: The following adverse reactions occurred more frequently than 1 in 100.

Gastrointestinal: stomatitis, anorexia, epigastric distress,* nausea,* constipation, abdominal discomfort, flatulence, diarrhea, abdominal pain, indigestion

Hematological: decreases in hemoglobin* and hematocrit* (see PRECAUTIONS), anemia, leucopenia, eosinophilia

Dermatologic: pruritus, rash

Central Nervous System: dizziness, somnolence, vertigo

Urogenital: BUN and creatinine elevations (see PRECAUTIONS)

Body as a Whole: headache, malaise

Special Senses: tinnitus

Cardiovascular/Respiratory: edema (see PRECAUTIONS)

* Reactions occurring in 3% to 9% of patients treated with FELDENE

Reactions occurring in 1% to 3% of patients are unmarked.

Incidence Less Than 1% (Causal Relationship Probable): The following adverse reactions occurred less frequently than 1 in 100. The probability exists that there is a causal relationship between FELDENE and these reactions.

Gastrointestinal: liver function abnormalities, jaundice, hepatitis (see PRECAUTIONS), vomiting, hematemesis, melena, gastrointestinal bleeding, perforation and ulceration (see WARNINGS), dry mouth

Hematological: thrombocytopenia, petechiat rash, ecchymosis, bone marrow depression including aplastic anemia, epistaxis

Dermatologic: sweating, erythema, bruising, desquamation, exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, vesiculo bullous reactions, photoallergic skin reactions

Central Nervous System: depression, insomnia, nervousness

Urogenital: hematuria, proteinuria, interstitial nephritis, renal failure, hyperkalemia, glomerulitis, papillary necrosis, nephrotic syndrome (see PRECAUTIONS)

Body as a Whole: pain (colic), fever, flu-like syndrome (see PRECAUTIONS)

Special Senses: swollen eyes, blurred vision, eye irritations

Cardiovascular/Respiratory: hypertension, worsening of congestive heart failure (see PRECAUTIONS), exacerbation of angina

Metabolic: hypoglycemia, hyperglycemia, weight increase, weight decrease

Hypersensitivity: anaphylaxis, bronchospasm, urticaria/angioedema, vasculitis, "serum sickness" (see PRECAUTIONS)

Incidence Less Than 1% (Causal Relationship Unknown): Other adverse reactions were reported with a frequency of less than 1 in 100, but a causal relationship between FELDENE and the reaction could not be determined.

Gastrointestinal: pancreatitis

Dermatologic: onycholysis, loss of hair

Central Nervous System: akathisia, hallucinations, mood alterations, dream abnormalities, mental confusion, paresthesias

Urogenital System: dysuria

Body as a Whole: weakness

Cardiovascular/Respiratory: palpitations, dyspnea

Hypersensitivity: positive ANA

OVERDOSAGE: In the event treatment for overdosage is required, the long plasma half-life of piroxicam should be considered. The absence of experience with acute overdosage precludes characterization of sequelae and recommendations of specific antidotal efficacy at this time. It is reasonable to assume that the standard measures of gastric evacuation and general supportive therapy would apply. In addition to supportive measures, the use of activated charcoal may effectively reduce the absorption and reabsorption of piroxicam. Experiments in dogs have demonstrated that the use of multiple-dose treatments with activated charcoal could reduce the half-life of piroxicam elimination from 27 hours (without charcoal) to 11 hours and reduce the systemic bioavailability of piroxicam by as much as 37% when activated charcoal is given as late as 6 hours after administration of piroxicam.

ADMINISTRATION AND DOSAGE: Rheumatoid Arthritis, Osteoarthritis: It is recommended that FELDENE therapy be initiated and maintained at a single daily dose of 20 mg. If desired, the daily dose may be divided.

Dosage recommendations and indications for use in children have not been established.

More detailed professional information available on request.

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References: 1. Siegmeth W: Serum concentrations of piroxicam in relation to its clinical effect in patients with chronic polyarthritis (trans). *Wien Med Wochenschr* 130:31-35, 1980. 2. Tausch: Placebo-controlled study of piroxicam in the treatment of rheumatoid arthritis. *Am J Med* (report) 72:18-22, February 16, 1982.

Pfizer **LABORATORIES DIVISION**
PFIZER INC.

(Continued from Page 170)

November 8-9—**Transurethral Ureterocopy: A Seminar and Workshop.** UCSD at La Jolla Marriott Hotel, San Diego. Saturday-Sunday. 13.5 hrs. Fee: $375. Contact: UCSD.

November 8-10—**State of the Art Urology—Live Television Coverage of Surgery.** UCLA at Miramar Sheraton Hotel, Santa Monica. Saturday-Monday. 21 hrs. Fee: $400. Contact: UCLA.

November 10-12—**Selected Topics in Endocrinology and Metabolism.** LLU at Ahwahnee Hotel, Yosemite. Monday-Wednesday. 12 hrs. Fee: $225. Contact: LLU.

December 27-January 1—**Advances in Internal Medicine.** University of Washington at Kauai Sheraton, Kauai. Saturday-Thursday. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle 98195. (206) 543-1050.

January 14—**Urology Update.** LLU at LLU. Wednesday. 7 hrs. Fee: $60. Contact: LLU.

OB/GYN

September 10—**Gynecology/Obstetrics: Update on the High Risk Pregnancy.** LLU at LLU. Wednesday. 3 hrs. Fee: $60. Contact: LLU.

October 2-5—**Advance Fetal Heart Monitoring.** UCI at Napa Valley. Thursday-Sunday. Contact: UCI.

October 10-11—**OB/GYN Ultrasound and Sonography—Update.** Sacramento Radiology Research and Education Foundation and Northern California Radiology Society. Friday-Saturday. 10 hrs. Fee: $125. Contact: John P. McGahan, MD, Sacramento Radiology Research and Education Foundation, PO Box 19184, Sacramento 95819.

October 20-24—**16th Annual Review Course in Obstetrics and Gynecology.** USC at Pasadena Hilton Hotel. Monday-Friday. 38 hrs. Fee: $545. Contact: USC.

October 20-24—**Comprehensive Review Course and Annual Postgraduate Course.** UCSF at San Francisco Hilton Hotel. Monday-Friday. 32 hrs. Fee: $525. Contact: UCSF.

October 20-25—**9th Annual Review Course in Clinical Obstetrics and Gynecology and/or Gynecological Histopathology.** UCI at Westin South Coast Plaza, Costa Mesa. Monday-Saturday. 17-46.5 hrs. Contact: UCI.

October 25—**Review Course for Gynecologic Pathology.** USC at Pasadena Hilton Hotel. Saturday. 6 hrs. Fee: $105. Contact: USC.

November 1-2—**Changing Trends in Gynecologic Practice.** UCI at Rancho Mirage. Saturday-Sunday. 10 hrs. Contact: UCI.

December 4-7—**Current Issues in Perinatal Medicine.** UCI at Desert Princess Hotel, Palm Springs. Thursday-Sunday. Contact: UCI.

December 11-13—**Advanced Ultrasound.** American College of OB/GYN at Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. 16 hrs. Contact: ACOG, 600 Maryland Ave SW, Ste 300 East, Washington, DC 20024-2588. (202) 863-2542.

January 16-18—**Gynecology Update for the Primary Care Physician.** UCSD at Vacation Village Resort, San Diego. Friday-Sunday. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

OPHTHALMOLOGY

September 17-18—**Lasers in Ophthalmology.** UCI at UCI. Wednesday-Thursday. 13 hrs. Contact: UCI.

December 11-12—**An Update in Neuro-Ophthalmology.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Friday. Contact: UCSF.

PATHOLOGY

September 10-12—**Cardiovascular Pathology.** STAN at STAN. Wednesday-Friday. Contact: STAN.

October 20-25—**9th Annual Review Course in Clinical Obstetrics and Gynecology and/or Gynecological Histopathology.** UCI at Westin South Coast Plaza, Costa Mesa. Monday-Saturday. Contact: UCI.

October 25—**Review Course for Gynecologic Pathology.** USC at Pasadena Hilton Hotel. Saturday. 6 hrs. Fee: $105. Contact: USC.

PEDIATRICS

September 4-5—**Pediatric Trauma 1986: The Practice and Controversies.** San Diego Children's Hospital at Hotel Inter-Continental, San Diego. Thursday-Friday. Fee: $400. Contact: Unconventional, Inc, PO Box 33185, San Diego 92103. (619) 692-9115.

September 8-10—**Pediatric Flexible Bronchoscopy.** UCD at UCD. Monday-Wednesday. 21 hrs. Contact: UCD.

September 11-13—**Pediatric Flexible Bronchoscopy.** UCD at UCD. Thursday-Saturday. 21 hrs. Contact: UCD.

September 24-25—**43rd Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at the Hilton Hotel, Los Angeles. Wednesday-Thursday. Contact: Eve Black, PO Box 2022, Inglewood 90305. (213) 757-1198.

September 26-28—**Advances in ENT, Allergy, and Infectious Diseases for the Practicing Physician.**

American Academy of Pediatrics at Sheraton Palace, San Francisco. Friday-Sunday. 16 hrs. Fee: $330. Contact: AAP, Neal A. Baker, Division of Continuing Education, PO Box 927, Elk Grove Village, IL 60007. (800) 433-9016, or in Illinois (800) 421-0589.

October 16-18—**Practical Topics in Pediatric Nutrition.** UCSF. Thursday-Saturday. 13 hrs. Fee: $300. Contact: UCSF.

October 24-25—**Pediatric Symposium.** Kaiser Permanente Medical Group at Biltmore Hotel, Los Angeles. Friday-Saturday. 12 hrs. Fee: $150. Contact: Judy Harrison, Dept of Clinical Services, Southern California Permanente Medical Group, 393 E Walnut St, Pasadena 91188. (818) 405-5000.

October 25-November 1—**Pediatrics for the Practitioner.** UCI at Mauna Kea Hotel, Hawaii. One Week. Contact: UCI.

October 31-November 1—**Paroxysmal Disorders of Childhood.** UCSF at Mark Hopkins Hotel, San Francisco. Friday-Saturday. 7 hrs. Fee: $150. Contact: UCSF.

November 13-15—**New Approaches in Children's Orthopaedics.** UCD at Monterey Plaza, Monterey. Thursday-Saturday. 9 hrs. Fee: $340. Contact: UCD.

November 21-24—**American Academy of Pediatrics Las Vegas Seminars.** Caesars Palace, Las Vegas. Friday-Monday. Contact: AAP, (213) 757-1198.

January 19-21—**Pediatrics for the Primary Care Physician.** UCSD at Vacation Village Resort, San Diego. Monday-Wednesday. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 24-31—**Pediatric Emergencies.** Scripps Memorial Hospital, Encinitas at Kona Surf Resort, Hawaii. One Week. 21 hrs. Fee: $375. Contact: Edith Bookstein/AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

January 30-February 1—**25th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Marriott Hotel. Friday-Sunday. 15 hrs. Fee: $175. Contact: Wayne Herbert, MD, Children's Hospital of Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

PSYCHIATRY

October 24-26—**1986 Self-Psychology Conference: Clinical Advances in Self-Psychology.** UCSD at Vacation Village Resort, San Diego. Friday-Sunday. 16.5 hrs. Fee: $275. Contact: UCSD.

December 28-January 3—**Psychiatry and the Practicing Physician—"New Year '87—Maui."** Hawaii Medical Association at Royal Lahaina Resort, Kaanapali Beach, Maui. Sunday-Saturday. 16.5 hrs. Fee: $385. Contact: Joe Harrison, MD, Symposium Maui, Inc, PO Box 10185, Lahaina, HI 96761. (808) 879-8182.

RADIOLOGY

August 25-28—**Annual Napa Valley Radiology Conference.** Sacramento Radiology Research and Education Foundation and the Northern California Radiology Society at Silverado Inn, Napa. Monday-Thursday. 20 hrs. Fee: $360. Contact: John P. McGahn, MD, Sacramento Radiology Research and Education Foundation, PO Box 19184, Sacramento 95819.

August 25-29—**Radiology.** USC at Kaui, Hawaii. Monday-Friday. 27 hrs. Fee: $535. Contact: USC.

September 2-5—**2nd Annual Physics and Biology of Radiology.** UCSD at Town and Country Hotel, San Diego. Tuesday-Friday. 28 hrs. Contact: R. Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

September 6—**Radiology.** Kaiser Permanente Medical Group at Disneyland Hotel, Anaheim. Saturday. 7.5 hrs. Fee: $100. Contact: Judy Harrison, Dept of Clinical Services, Southern California Permanente Medical Group, 393 E Walnut St, Pasadena 91188. (818) 405-5000.

September 6-7—**Head and Neck Radiology.** UCSF at San Francisco Hyatt Regency. Saturday-Sunday. Contact: UCSF.

September 8-12—**Clinical Magnetic Resonance Imaging.** UCSF at San Francisco Hyatt Regency. Monday-Friday. Contact: UCSF.

September 12-14—**Sonographers' Update and Review.** UCSD at Hanalei Hotel, San Diego. Friday-Sunday. 20 hrs. Contact: R. Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

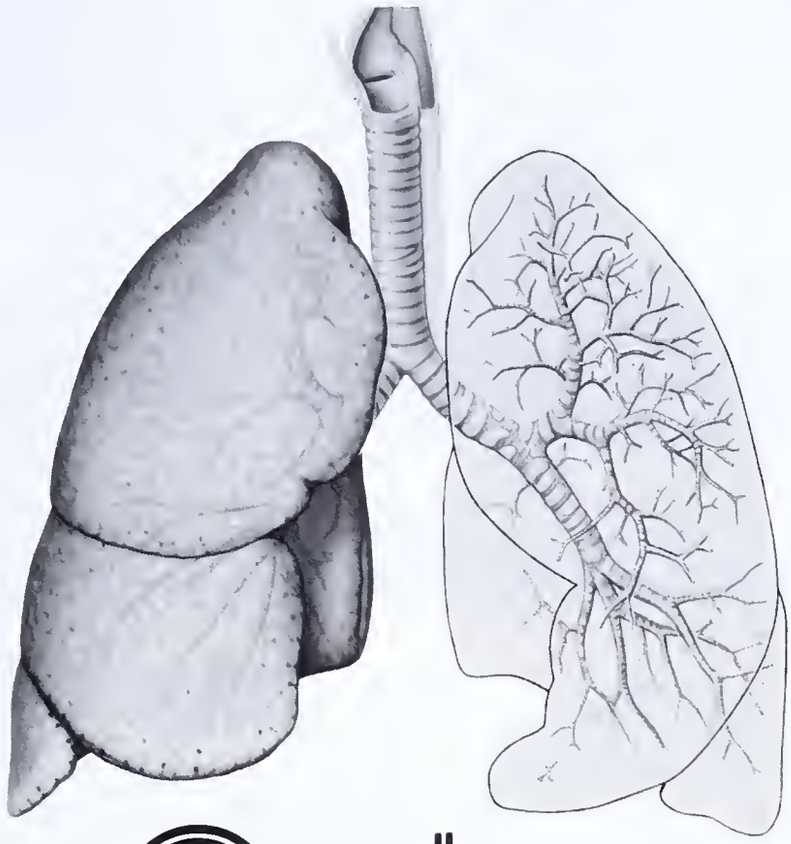
September 24-26—**Interventional Radiology Tutorial: Non-Vascular Techniques.** Sharp Memorial Hospital, San Diego at Hyatt Islandia, San Diego. Wednesday-Friday. Contact: Elizabeth Douglas, Seminar Coordinator, 7901 Frost St, San Diego 92123. (619) 541-3206.

October 6-10—**11th Annual San Diego Postgraduate Radiology Course.** UCSD at the Hotel Del Coronado, San Diego. Monday-Friday. 24 hrs. Fee: $425. Contact: R. Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

October 10-11—**OB/GYN Ultrasound and Sonography—Update.** Sacramento Radiology Research and Education Foundation and Northern California Radiology Society. Friday-Saturday. 10 hrs. Fee: $125. Contact: John P. McGahan, MD, Sacramento Radiology Research and Education Foundation, PO Box 19184, Sacramento 95819.

(Continued on Page 178)

Consider the causative organisms...



Ceclor®
cefaclor

250-mg Pulvules® t.i.d. offers effectiveness against the major causes of bacterial bronchitis

Haemophilus influenzae*, *H influenzae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes
(ampicillin-susceptible) (ampicillin-resistant)

Note: Ceclor® is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

Ceclor® (cefaclor)

Summary. Consult the package literature for prescribing information.

Indications: Lower respiratory infections, including pneumonia, caused by susceptible strains of *Streptococcus pneumoniae, Haemophilus influenzae,* and *S. pyogenes* (group A beta-hemolytic streptococci).

Contraindications: Known allergy to cephalosporins.

Warnings: CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:

- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- In renal impairment, safe dosage of Ceclor may be lower than that usually recommended. Ceclor should be administered with caution in such patients.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include:

- Gastrointestinal (mostly diarrhea): 2.5%.
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, erythema multiforme, serum-sickness-like reactions): 1.5%; usually subside within a few days after cessation of therapy. These reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.
- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1%.

Abnormalities in laboratory results of uncertain etiology

- Slight elevations in hepatic enzymes.
- Transient fluctuations in leukocyte count (especially in infants and children)
- Abnormal urinalysis; elevations in BUN or serum creatinine
- Positive direct Coombs' test
- False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (glucose enzymatic test strip, Lilly)

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Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285

Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630

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Physicians Address the Issues at the Utah State Medical Association

Annual Meeting

U.S.M.A. UTAH STATE MEDICAL ASSOCIATION

September 10, 11, 12, 1986
The Yarrow Resort
Park City, Utah

Physicians Address the Issues at the Utah State Medical Association ANNUAL MEETING

September 10, 11, 12, 1986, **The Yarrow Resort,** Park City, Utah

WEDNESDAY, SEPTEMBER 10

8:00 AM Young Physicians Section

9:00 AM Hospital Medical Staff Section

9:30 AM USMA House of Delegates Opening Session

12:00 NOON Luncheon
Speaker: John J. Coury, Jr, MD
President
American Medical Association

1:30 PM Reference Committee Meetings

4:00 PM USMA House of Delegates

7:30 PM Barbecue

THURSDAY, SEPTEMBER 11

7:00 AM Fun Run—3K and 10K Races

9:00 AM **Converging Pressures: A Changing Profession Forum on Medical Issues**

Entrepreneurialism and Professionalism: When Do They Conflict?
George D. Lundberg, MD, Editor
Journal of American Medical Association

A Federal Solution to the Malpractice Crisis
David N. Sundwall, MD, Staff Assistant
Labor & Human Resources Committee
U.S. Senate

Making Decisions Washington Style: The Doctor's Dilemma
John C. Nelson, MD
Commissioner
Federal Prospective Payment Assessment Commission

Physician Alternatives in Health Care Delivery
Allan H. Goodman, MD
Chairman of the Board
Western Health Plans, Inc.
San Diego, California

12:00 NOON *Luncheon Speaker:*
Ambassador David Kennedy

AFTERNOON Golf—Tennis

6:30 PM **Presidents' Dinner**

FRIDAY, SEPTEMBER 12

9:00 AM **Medical Problems With Social Consequences**

AIDS
Paul A. Volberding, MD
Chief, AIDS Activities Division
San Francisco General Hospital

Alzheimers
Murray Raskin, MD
Director for Geriatric Research, Education and Clinical Center
Seattle and American Lake VA Hospitals
(Speaker sponsored by Roerig-Pfizer Company)

Abuse of Children
Frederic N. Silverman, MD
Clinical Professor of Radiology
University of California, San Francisco

12:00 NOON Luncheon Meeting

Medical Liability Loss Prevention
Special training for Prevention Coordinators and practical information for doctors who wish to minimize risk of malpractice in their hospitals and offices.

John B. Stanchfield, MD
Medical Director
Utah Medical Insurance Association

REGISTRATION FORM:

Please return form with check by September 1, 1986, to Utah State Medical Association, 540 East Fifth South, Salt Lake City, Utah 84102.

Registration for:
☐ USMA members (not including luncheons): No Charge; ☐ Nonmembers: $50
Luncheons: ☐ Wednesday $10 ☐ Thursday $10 ☐ Friday $10
(USMA Delegates do not pay for Wednesday luncheon)
☐ Barbeque (per person) $10
☐ Presidents' Reception and Banquet (per person) $25

Total Amount Enclosed _____

Room Reservations: Contact The Yarrow Resort, P.O. Box 1840, Park City, UT 84060

Registration for Activities:
Please Send Sign-up Forms for the Following:
☐ 3K RACE OR 10K RACE ☐ GOLF TOURNAMENT ☐ TENNIS TOURNAMENT

CME Credit: Forum on Medical Issues—3 hours, Scientific Sessions—3 hours, Medical Liability Sessions—2 hours

(Continued from Page 174)

October 19-23—**11th Annual International Body Imaging Conference.** West Park Hospital at Kauai, Hawaii. Sunday-Thursday. Contact: 11th Annual Body Imaging Conference, 21915 Roscoe Blvd, Ste 222, Canoga Park 91304. (818) 701-5143.

October 25-29—**Radiology.** USC at Kauai, Hawaii. Saturday-Wednesday. 27 hrs. Fee: $535. Contact: USC.

October 30-November 1—**San Diego Imaging Symposium.** UCSD at US Grant Hotel, San Diego. Thursday-Saturday. 14 hrs. Contact: R. Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

November 3-7—**Diagnostic Radiology Seminars.** UCSF at Maui Marriott Hotel, Hawaii. Monday-Friday. Contact: UCSF.

December 11-13—**Advanced Ultrasound.** American College of OB/GYN at Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. 16 hrs. Contact: ACOG, 600 Maryland Ave SW, Ste 300 East, Washington, DC 20024-2588. (202) 863-2542.

January 9-12—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz Carlton Hotel, Laguna Niguel. Friday-Monday. Contact: UCSD.

January 13-16—**Chest Radiology—1987.** UCSD at Hotel Del Coronado, San Diego. Tuesday-Friday. Contact: UCSD.

January 16-18—**Annual Update on Nuclear Radiology.** UCSD at Hotel Del Coronado, San Diego. Friday-Sunday. Fee: $400. Contact: R. Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 22-24—**Practical Approach to Duplex Imaging.** UCSD at San Diego Hilton Hotel. Thursday-Saturday. Contact: UCSD.

SPORTS MEDICINE

August 16-23—**Effective Diagnosis of Common Sport Injuries.** University of Arizona at Otter Bar Lodge, Forks of Salmon (near Eureka). One Week. Contact: Epic Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

November 25-28—**Sports Medicine.** American College of Sports Medicine and Children's Hospital Medical Center, Oakland at Inter-Continental Hotel, Maui. Tuesday-Friday. 25 hrs. Fee: $300. Contact: Stuart Zeman, MD, Course Chairman, 2999 Regent St, Ste 203, Berkeley 94705. (415) 540-8686.

December 10—**Orthopedic Surgery: Sports Injuries.** LLU at LLU. Wednesday. 6 hrs. Fee: $60. Contact: LLU.

SURGERY

September 13—**8th Annual Plastic Surgery Symposium.** Los Angeles Society of Plastic Surgeons at Marina City Club, Marina Del Rey. Saturday. Contact: Patricia Watner, LA Society of Plastic Surgeons, 2001 Santa Monica Blvd., Ste 1180 W, Santa Monica 90404.

September 27-October 4—**Temporal Bone Surgical Dissection and Cochlear Implant.** Los Angeles House Ear Institute. One Week. 62 hrs. Fee: $900. Contact: Antonio De La Cruz, MD, House Ear Institute, 256 South Lake St, Los Angeles 90057. (213) 483-4431.

September 28-October 1—**Preparing Patients for Surgery.** American College of Physicians and UCD at Monterey Hyatt Regency. Sunday-Wednesday. 14.75 hrs. Contact: ACP, Maxine Topping, (800) 523-1546, ext 207.

October 6-10—**4th Annual UCLA Symposium: A Comprehensive Review of Vascular Surgery.** Miramar-Sheraton Hotel, Santa Monica. Monday-Friday. 35 hrs. Fee: $595. Contact: UCLA.

October 11—**Lumbar Spine and Pelvis.** UCSD at the Hotel Del Coronado, San Diego. Saturday. 7 hrs. Fee: $150. Contact: R. Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

October 18-19—**1986 Regional Review Course in Hand Surgery.** American Society for Surgery of the Hand at Orthopaedic Hospital, Los Angeles. Saturday-Sunday. 12 hrs. Fee: $200. Contact: American Society for Surgery of the Hand, 3025 S Parker Rd, Ste 65, Aurora, CO 80014. (303) 755-4588.

October 18-25—**8th International Seminar on Operative Arthroscopy.** UCLA at Maui, Hawaii. One week. Contact: UCLA.

October 18-25—**Temporal Bone Surgical Dissection and Cochlear Implant.** House Ear Institute, Los Angeles. One Week. 62 hrs. Fee: $900. Contact: Antonio De La Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

October 24-26—**The Practical Applications of Recent Advances in Neurosurgery Research.** Scripps Clinic and Research Foundation, La Jolla. Friday-Sunday. 16.5 hrs. Fee: $250. Contact: Dept of Academic Affairs, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

November 1-8—**Temporal Bone Surgical Dissection and Cochlear Implant Courses.** House Ear Institute. One week. 62 hrs. Fee: $900. Contact: Antonio De La Cruz, MD, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

November 10-14—**Cochlear Implant.** House Ear Institute. Monday-Friday. 32 hrs. Fee: $1,350. Con-

(Continued on Page 273)

FHP is a leading HMO that has specialized in quality, prepaid healthcare for over 25 years. Our continued expansion and the recent opening of our new 117-bed hospital have created openings for Board Certified or Board Eligible physicians in both primary care and specialty areas. Practicing with FHP offers physicians a unique opportunity to experience the advantages of private practice without the administrative headaches. FHP physicians enjoy excellent benefits, which include:

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Fountain Valley, CA 92708

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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The Western
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The Aim of American Medicine Within the Constraints of Today's Society

WHAT SHOULD BE the aim of American medicine within the constraints of today's society? These are times of great change in health care, and American medicine is inescapably a part of this change. Since the turn of the century this nation has been able to give better health care to more people than had ever been possible before. The aim of American medicine was to promote this new scientific medicine, and this was clear enough and was generally accepted. Progress in medical science and public support of it, and of the skills and wherewithal to deliver modern scientific care, made this achievement possible. But now this success has a down side. The costs have come to be considered unacceptable, and a host of new ethical, moral and legal questions have been raised, most of which have yet to be resolved. All of this has led society to place unprecedented constraints upon physicians and health care, constraints that increasingly impinge upon what takes place between doctors and their patients and affect the actual care of patients in many ways.

Every known human society has had some form of medicine and it would seem that medicine somehow fills a very deep human need. If so, then should the aim of medicine be to fill this need, and if this is so, then just what is this need? Is it for practical aid and personal comfort in the face of the fear or reality of pain, serious disability or death, or even mere physical or mental discomfort, or—perhaps just as important—for some help in contending with the reality of life? The "horse and buggy doctor" shared illness and death and anxiety and hope with patient and family, and gave solace and strength to both through his authority as a physician, and he was loved and revered.

Just as modern medical science and new medical technology have had profound social, economic and political effects upon society as a whole, so have the responses of society in the form of social, economic and political pressures and constraints profoundly affected medicine and health care in this nation. There is a new and complex interdependence among all the parties at interest in health care, and a new need to try to clarify and agree upon the aim of medicine as this relates to the needs of patients and the health care of society as a whole.

The editors of *The Western Journal of Medicine* propose to provide a forum for dialogue and discussion of the aim and purpose of medicine within the constraints now being placed on health care. The forum is initiated with the statements beginning on the following pages. Readers and others are invited to submit their views constructively and succinctly. As many as space permits will be published in future issues of the journal. At an appropriate time all the material will be collated and, if possible, the distillate will be prepared as a statement on "The Aim of American Medicine Within the Constraints of Today's Society."

MSMW

Ancient Tenets, Contemporary Meaning

ALBERT R. JONSEN, PhD, *San Francisco*

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"CONSTRAINT" is a catchword of the age of scarce resources. We readily speak of the "the constraints of our financial situation" or "the constraints imposed by the deficit." Yet catchwords, as their name suggests, catch up into a conceptual cloud many nuances and obscure more precise meanings. They are "commonplace"—words that are familiar and immediately understood, yet comprehended only shallowly and partially. If we look at "constraint" more closely, we find that it comes from the Latin *stringere*, which means "to draw tight, to bind." In this, it is like "restraint." But unlike "restraint," "constraint" shares with many other words, like "conscience" and "consent," the prefix "con"—meaning "with" or "together" and implying something shared, held in common.

Thus, I prefer to use "constraint" to describe the common bonds of values and principles that *bind together* a society or a group within a society, like a profession. Indeed, in its early English uses, "constraint" seems generally to refer to the obligations of conscience; "restraint" applies more properly to external bonds or limits. A person is constrained by a duty or responsibility; a horse is restrained by a tether or a fence.

What does this refined nicety of verbal usage have to do with the theme of this forum? From my point of view, one question to be asked is "how can the constraints of medical ethics—that is, the obligations and responsibilities of medical practice—meet the restraints of financial limits, legal restrictions, social barriers?" Some might quickly answer that medical ethics must simply reform so that its internal constraints respond to—and mirror—the external demands. Others will adamantly reject the question, saying medical ethics must stand firm against the pressures thrusting upon medicine from without. Both views are inadequate: the first simply abolishes the unique and traditional role of medicine; the second initiates conflict between social functions that must cooperate.

A proper response must carefully examine the nature and limits of the various tenets of medical ethics in view of the economic, social and legal realities. Prolonging life, preserving confidentiality, refraining from harm, promoting the patient's benefit rather than one's own or others'—each of these tenets has a long history. Each of these has meaning that derives from the social, economic and legal context of medicine's evolution. The capabilities of physicians were interpreted within the cultural and social values of successive eras. The ethics of medicine we have today reflects that past. It contains enduring values. It will move into the future by discovering how those enduring values can be realized in new social and cultural contexts.

Thus, modern medical ethics, which has developed into a unique discipline within the last decade, does more than repeat the ancient tenets. It asks how a careful examination of those tenets might reveal their contemporary meaning. Occasionally, it will reveal that some tenet has outlived its usefulness: the ancient rule that required physicians to hide from a patient any information about diagnosis and prognosis has fallen before the new rule that requires "informed consent," a rule that reflects the modern ethics of personal autonomy. More frequently, the work of medical ethics has been to reveal the limits of some enduring tenet. The imperative "prolong life" arose when the skill of stopping a hemorrhage could save a life; it must be refined when medical technology can sustain organic processes after human consciousness or human communication are irretrievably lost.

The next task of medical ethics will be to examine how the ancient tenet of dedication to the welfare of one's patient can be preserved at a time when the financial and social organization of medical care takes new forms. How does a physician remain the patient's advocate in circumstances in which the relationship may be highly impersonal, financially unprofitable, legally threatening? Should a physician's ethic of

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Reprint requests to Albert R. Jonsen, PhD, Chief, Division of Biomedical Ethics, University of California, San Francisco, 1326-3rd Avenue, San Francisco, CA 94143.

absolute dedication to a patient yield before a policy that rations care in particular ways? Should physicians serve as gatekeepers into the house of care? These questions arise from ancient principles as yet untested and untried in the current world. They may sound like paradoxes—problems without solution—but they are, more likely, problems still unexamined. The constraints of a physician's conscience must not be relaxed in face of social restraints, but rather refined to discover the essential values of competent, humane and responsible care in a just and orderly society.

Cut the Cost, Keep the Care

GEORGE E. POLLOCK, ***Edmonds, Washington***

State Director, Washington, American Association of Retired Persons, Edmonds, Washington

IN POSING THE QUESTION of this forum (What should be the aim of American medicine within the constraints of today's society?), there is the supposition that somehow efforts to contain skyrocketing costs change society's expectations of the medical profession. In the view of the American Association of Retired Persons (AARP), no such change has occurred. In fact, the slogan of our nationwide health care consciousness-raising campaign is "Cut the Cost, Keep the Care." And that is not only what we expect, but what we will demand. Implicit in our goal is our belief that the medical industry cannot justify cost increases that in 1983 were 2½ times the rate of growth in other goods and services. And that was not an aberrant year. In fact, between 1967 and 1983 when the Consumer Price Index (CPI) for all items rose by 198%, the medical care component of the CPI increased by a whopping 257%!

So to cope with inflation that was putting health care out of the reach of millions of poor and uninsured Americans and bringing Medicare to the brink of bankruptcy, Congress put hospitals on an allowance. We think it likely that lawmakers will put doctors on a similar diet soon. At the same time, it is erroneous to say society will be willing to accept a reduced standard of care. The "aim of American medicine" today should be to discover new ways to provide high quality care at affordable prices.

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And, in considering new approaches, such as prospective pricing and Diagnosis Related Groups, we must ask ourselves the following questions:

- What is high quality care?
- How can quality be measured?
- How can we assure high quality care in an environment of cost cutting?

We have taken the first few steps toward trying to answer the tricky question of quality through peer review organizations. Despite the existence of PROs, we are disturbed by numerous reports of inadequate care of elderly Medicare patients since the onset of prospective payment. In their zeal to keep profits—or so-called operating margins—high, some hospitals have been discharging elderly patients prematurely. Early discharge incentives in the prospective payment system were acknowledged as the system was begun, but the eagerness with which hospitals have been showing older patients the door has been shocking. It was not too long ago that assertions by AARP and others of premature discharge problems were being dismissed as alarmist or anecdotal. We still do not have an adequate grasp of the extent of the problem, and we recognize that not all early discharges are premature or against the patient's interest. But AARP will insist upon significantly increased vigilance and evidence that the threat of premature discharge is being taken seriously. However, society cannot look to PROs to accept the total burden for quality care. Doctors, nurses, administrators and discharge planners must take their share of responsibility for the task.

While the issue of premature discharges is important in and of itself, it must also be viewed in a broader context. We

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are experiencing a stampede toward reductions in health care delivery. Everywhere we look, insurers, review organizations and new health delivery systems are touting their ability to reduce utilization. The word "unnecessary" has taken on the quality of a meditation mantra. But before policymakers break out the champagne and toast the lower rate of health care inflation, society must make sure this new system is not backfiring. Washington must make sure that it is not breaking the historic Medicare promise made to our senior citizens 20 years ago.

AARP members say, yes, reduce the unnecessary surgery, avoidable deaths and truly unnecessary hospital days—but do it in the name and for the sake of quality of care and be ready to stand up and say to all concerned: This patient and that patient and that patient are not ready to be left unattended.

While the initial focus of quality review is on hospital inpatients, examination must *not* be limited to just the inpatient setting. Reductions in the length of stay, increases in patient transfers and greater use of outpatient services all point to the need for studying quality and the outcomes of care after discharge. Moreover, physical functioning, emotional wellness and capacity for independent living—including the effect of the prospective payment system on family members—are all crucial dimensions of care that must be understood. Finally, AARP will continue to press for a stronger consumer role in determining changes in the health care system and then educating the public about those changes.

So, in summary, it is AARP's position that the aim of the American medical system must remain as it historically has been—the provision of the best medical care in the world to all who are in need of it, regardless of their ability to pay. The only change that today's society has dictated is that some new and innovative ways to deliver that care must be developed.

A Healthy, Disease-Free Society

FRANK G. MOODY, MD, *Houston*
Professor and Chairman, Department of Surgery, The University of Texas Medical School at Houston

THE PACE OF CHANGE in the way medicine is practiced in the United States has generated a sense of anxiety in providers of health care, their patients and the health care establishment in general. This uneasy mood is derived from the perception on the part of government and the private sector that medical care, as it is currently provided, is too expensive. There unfortunately are few data upon which to make an objective judgment about whether the public, as represented by the government or industry, is getting its money's worth. Little is written or discussed as to what the inflated health dollar buys. What is clear is that the payors want a cheaper product and more accountability. The obvious risk to cost cutting is a dramatic and potentially harmful decrease in the quality and access to health care.

The responses to fiscal restraint include Medicare's diagnosis related groups (DRGs), proliferation of health maintenance organizations (HMOs), encouragement of competitive medicine through for-profit conglomerates and, more recently, "verticalization" of care in which a hospital develops its own medical catchment area. What is bewildering is that all these things are happening at once.

How should American medicine respond to these profound changes in the way in which sick people are cared for? If the trend towards institutionalized medicine continues at its current rate, it is clear that most physicians will be working in association with other physicians for a corporate entity. An effort is under way to preserve the traditions of private practice with its fee-for-service compensation and the close doctor-patient relationship in the form of independent practice associations (IPAs). It is unlikely, however, that this mode of care will be able to compete with the more efficient, and apparently cheaper, comprehensive care practiced by large prepaid multidisciplinary groups.

But economics is not the only issue. The public cannot be denied the benefits of a rapidly evolving body of knowledge

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Reprint requests to Frank G. Moody, MD, Professor and Chairman, Department of Surgery, The University of Texas Medical School at Houston, 6431 Fannin Street, Houston, TX 77030.

and technology. Medicine's aim should clearly be to bring therapies to the sick that will relieve their suffering or cure their ills. More important, a larger effort should be made toward understanding human behavior and the origins of disease. The prevention of cardiovascular disease, cancer and traumatic injury would clearly represent cost savings and a positive contribution to the quality of human life. I am convinced that this is an ideal that likely could be achieved within this century if more effort and resources were devoted to it. Not that all of our ills would be prevented, nor would there be perpetual life on earth, but at least incapacitating illness could be reduced to a minimum.

Meanwhile, more attention must be paid to enhancing the flow of ideas from the bench to the bedside. This will require a more concerted integration of the knowledge-generation potential of universities and the production and distribution capacity of industry. Government has an important role in the process through supporting higher education for its constituents and for insuring a legal climate in which new technology can be applied without excessive liability. A healthy, disease-free society must remain the ultimate goal whether we can afford it or not. In my opinion, there is adequate money available for this purpose. It only remains that it be used wisely.

The Essence of Being a Physician

JACOB NEEDLEMAN, PhD, *San Francisco*
Professor, Department of Philosophy, San Francisco State University, San Francisco

AT A DINNER PARTY the other night, I happened to be seated next to a young, energetic health care consultant who challengingly asked me about my book *The Way of the Physician*. She wanted to know what a professor of philosophy and comparative religion could possibly say of practical use in the current crisis facing the medical profession. In light-hearted, dinner-party tones, but with quite serious intent, I explained the thesis of my book: that doctors have to become *people* and that nothing else will rescue modern medicine from its present difficulties. I was taken aback by her reply. Without a moment's hesitation, she said flatly that such a thing was not possible! The role of a doctor was now, she maintained, to serve solely as a scientific technician. A patient's need for compassion and humane attention was far better met by a nurse practitioner or a chaplain or a social worker. Doctors, in the familiar sense of the term, no longer exist. So she said.

Is it true? Are we actually entering the "postphysician era" in which the ancient, archetypal function of a doctor will now be parceled out among medical technicians and paramedical professionals? I do not think so. But to rediscover the meaning of being a physician within the constraints of today's society will require that we know with certainty the essence of the practice of medicine, the essence of what it means to be a physician. The role of physician is fundamental to human society and culture. In one mode or another, this role has always existed. It represents the blending within the human psyche of knowledge and love, the mysterious but necessary balance between mind and heart, scientific detachment and compassionate engagement in the suffering of our fellow human beings.

I maintain that the constraints of today's society have no intrinsic power to prevent our moving toward this ideal. In fact, much of what now seems to block this ideal—the economic, legal and governmental forces—owe their power solely to our failure to perceive the essence of the physicians' art. It may be true that in many respects today's physicians cannot outwardly conduct their practices in ways that were once taken for granted. But the inner reality of the art of medicine remains the same, and by holding fast to that inner reality we can, I believe, regenerate the role of doctor and infuse life into the forms of medical practice that are dictated by contemporary socioeconomic influences. At the same

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time, no amount of policy-making, lobbying, technological innovation or making of political and financial alliances will stem the onrushing tide of the "postphysician era" without our understanding that inner reality.

Now comes the difficult part. What is the essence of the physician's art? The difficulty of this question is that the answer is so obvious. The heart of medicine is surely the personal, direct transaction between doctor and patient. The heart of medicine is the time, be it measured in minutes or hours, that a physician is face-to-face with the person who needs his or her help. In that transaction, the one essential thing that the doctor can give the patient is attention. Simple. Obvious. And yet, not so simple after all. My studies of the spiritual history of humanity have shown me that the power that we so loosely call attention is today our most undeveloped faculty. To put it baldly, the quality of human attention has degenerated in our era almost in direct proportion to the advances we have made in scientific technology. The power of attention, the power to listen, to be present, to allow all the sources of perception within us to move out toward another human being, the power to be silent when necessary, to allow thoughts (which are not the same thing as attention) to combine creatively—all this, and more, is what the ancient wisdom understood as the real power of the human mind. The modern era has made a grave error in identifying mind with the process of merely combining thought associations. The development of the power and willingness to listen—to the patient and to oneself—is the essence of the art of medicine. By the way, it is also the essence of the art of living itself.

There are ways to cultivate and develop this power, but they are not and may never be part of a medical school curriculum. Space does not allow more to be said here about these methods. All that I wish to assert is that upon the cultivation of this power of the mind and heart depends the good or bad uses of scientific technology and the extent to which we modern people cave in or stand up to the bewildering external changes in the world around us.

We are all physicians.

Medicine's Aims, Society's Constraints

JAMES O. MASON, MD, *Atlanta*
Director, Centers for Disease Control, Atlanta

THE FUNDAMENTAL AIM of American medicine is to contribute to the fullest possible extent to the health of all people. This primary purpose does not change from year to year, or from decade to decade. It was valid a century ago, at a time of limited tools and limited expectations. It is true today, at a time when our technological capabilities have grown spectacularly, and society's expectations may perhaps have grown more rapidly still.

It is evident that American medicine, in common with American society as a whole, will be experiencing tight economic constraints in the years ahead. Public sector expenditures for health will clearly be restricted, as increasingly stringent controls are placed on federal dollars. Therefore, it is particularly timely that American medicine should reexamine not its time-honored purpose but rather the priorities and modalities by which it seeks to achieve that aim.

In the recent past, we have been investing an ever-higher share of our gross national product in health, without apparent proportional gains in our national health status. It may well be that the concept of appropriate technology, which is receiving a great deal of attention in relation to health and medical programs in developing countries, has relevance for our situation as well.

Basically, the technology can be considered appropriate that

- stresses prevention of disease,
- seeks, to the greatest possible extent, treatment at primary rather than secondary and tertiary levels,

(Mason JO: Medicine's aims, society's constraints—*In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Aug; 145:186-187)

Reprint requests to James O. Mason, MD, Director, Centers for Disease Control, Atlanta, GA 30333.

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• involves patients and their families in both prevention and treatment and

• in general is truly economical in the sense of bringing the greatest good to the greatest number.

One set of criteria receiving increasing attention as a means of assessing priorities for health and medical investment is the concept of "years of potential life lost before age 65." It is a data class that gives greater weight to these causes of mortality that affect younger age groups. It emphasizes the human and social toll exacted by deaths in the early years. By doing so, this approach highlights the primacy of prevention and early intervention.

Using this measure, the Health Policy Project of the Carter Center at Emory University, in cooperation with the Centers for Disease Control, has estimated that nearly 65% of the years of potential life lost before age 65 are due to preventable causes, given full application of existing scientific and technical knowledge. This is an encouraging conclusion. But it poses a challenge to medicine and public health. It tells us we could be doing much more than we are.

Enormous differences in health status exist between the well served and the poorly served in our society, and the gaps account for the major share of those premature and preventable deaths. Most minority groups in the United States have more disease, both chronic and acute, and die at earlier ages than the white majority population.

The report "Black and Minority Health," recently issued by the Department of Health and Human Services, indicated that blacks under age 45 have an overall risk of death about twice as high as that for whites. Cancer incidence is 25% higher among black males than nonminority males, and black men are ten times more likely to die of hypertension. For the black male population as a whole, the average annual age-adjusted death rate for all causes in the years 1979-1981 was 1,084.6 per 100,000 as contrasted with 736.0 for white males. For females, the corresponding figures are 611.7 for blacks and 405.0 for whites.

The Black and Minority Health Task Force report estimates an annual total of 60,000 "excess deaths" among minorities—deaths that would not occur if minorities had the same death rate as the nonminority population. Moreover, it needs to be borne in mind that this total does not include the large and rapidly growing Hispanic minority for whom figures on death rates are not available. Although not all of the factors contributing to these excess deaths can be directly acted upon by physicians, many can.

Reducing these excess deaths in our minority population—bringing their health status closer to the level we know we can achieve—would seem to be an appropriate target for American medicine in concert with society as a whole, in an era of constraints and cost-consciousness. By selecting and investing in technologies appropriate to the reduction of infant mortality, for example, we shall be adding many years to many lives rather than months to a few.

American medicine can fulfill its purpose in an era of constraint by closing the gaps between where we are and where we could be in terms of preventable morbidity, premature deaths and improved quality of life.

The Lessons of Finitude

H. TRISTRAM ENGELHARDT, Jr, PhD, MD, *Houston*

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THE FUNDAMENTAL GOALS of medicine remain the same as long as men and women suffer. Medicine evolved as a constellation of sciences and arts aimed at diminishing, curing and preventing pain, disability and deformity, as well as postponing death. Toward these ends elaborate accounts of disease and dysfunction have been developed, and medicine's concerns with care, cure and prevention are placed within ever more scientific and technological understandings of the complaints that bring patients to physicians. Still, the words of Hippocrates ring true: "Declare the past, diagnose the present, foretell the future; practice these acts. As to diseases, make a habit of two things—to help, or at least to do no harm."[1]

What has changed is the social context of medicine. The

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passage quoted from "Epidemics" continues: "The art has three factors, the disease, the patient, the physician. The physician is the servant of the art. The patient must cooperate with the physician in combating the disease." Much more is now involved. In addition to the disease, the patient and the physician, there are organized medicine, third-party payers and complicated governmental regulations and interventions, including both malpractice suits and cost-containment rules. Things are no longer the way they appeared to the author of the Hippocratic work "Law," who observed, "medicine is the only art which our states have made subject to no penalty save that of dishonor."[2] Even if the author understated the legal restrictions of ancient Greece, the practice of medicine experienced relatively few formal societal constraints.

In looking to the future, we will have to adapt the wisdom expressed in "Epidemics" to our current circumstances. We will need to determine how both third-party payers and governments can usefully "cooperate with the physician in combating the disease." Such reflections will need to be guided by a recognition that many of our current problems spring from our past attempts to act as good physicians and good citizens. The explosion of health care expenditures is traceable in great measure to the fact that it became easier to pay for health care just as health care was becoming more technologically sophisticated and more costly. The major growth in the proportion of the gross national product devoted to health care occurred over the last 30 years, as more of the population was covered by third-party payers, including Medicare and Medicaid. In 1950 and 1955 the percentage of the gross national product devoted to health care was 4.4, rising to 5.3 in 1960, to 6.1 in 1965, to 7.3 in 1970, to 7.8 in 1975, to 9.4 in 1980 and to about 10.8 in 1983.[3] A physician's traditional role of being concerned not to overexpend the resources of patients on marginally useful treatment was seriously weakened.

Organized beneficence and distribution of risks through insurance coverage have bred budget deficits and escalating insurance costs. The solution to the problem of individual access to health care has led to national problems of containing health care expenditures. As Alasdair MacIntyre once put it, our virtues can become vices.[4] Current difficulties with diagnosis related groups[5] and other forms of cost containment suggest that we are now creating new problems as we attempt to solve the problems engendered by third-party payment for medical care (problems that arose as we addressed the problem of access to health care in the 1950s and 1960s).

In the past, our culture provided a general endorsement of the notion that this life was not the only one and that it need not be held onto at all costs. To a great extent, such views are no longer a part of our official culture. We are consequently forced to shoulder the major moral project of setting limits to the proper use of health care resources with little or conflicting guidance from reigning cultural norms. We are confronted with the unpleasant circumstance of having lost the traditional Judeo-Christian restraints on duties to treat without having recaptured the temperance of our pagan ancestors, while at the same time the issues are muddied further by right-to-life rhetoric that often glosses over the traditional limits of duties to treat.

We will need to learn how morally to commit less than all available resources to saving life while maintaining the traditional goals of caring and curing.[6] This will lead not only to rethinking Baby Doe regulations and expanding natural death acts, but to the medical profession developing indications for the use of expensive as well as routine medical technology that more explicitly incorporate cost-effectiveness considerations. We as a society attempted to solve the problems of access to health care through privately and publicly funded health insurance. Physicians can help solve the problem of rising costs by helping society prudently to limit various forms of insurance coverage. How many, for example, would want to pay for insurance for intensive care unit services in the event they should develop Alzheimer's disease? Deciding where to deploy funds has major moral dimensions and requires good medical data. It is a task to which physicians can make a special contribution so that societal constraints can better serve patients' needs. Medicine as a learned profession should instruct concerning the lessons of finitude.

(Engelhardt HT Jr: The lessons of finitude—*In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Aug; 145:187-188)

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Corporate Profit or Public Good?

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THE ULTIMATE AIM of American medicine is to serve the health and medical needs of all people. Individual practitioners will continue to practice medicine on behalf of themselves, their patients and society, with the frequently conflicting objectives that those constituencies demand.[1] The difficult issue in the next decade is less the goals of American medicine and more the means through which those goals are to be accomplished: under what circumstances and under whose control will the health and medical needs of people be met?

In the 1960s there appeared to be a political consensus that access to health care was a right and choices were made to implement that right. The choice was not a single national health program but a series of programs aimed at priority targets—Medicare for the elderly, Medicaid for some of the poor, community health centers, National Health Service Corps in underserved areas—and to provide the personnel and knowledge necessary—federal support for health professions education, increased support of biomedical research, Regional Medical Programs, Area Health Education Centers.

These programs, together with private sector initiatives, improved equity of access: the poor and the elderly increased their physician visits; infant mortality rates declined dramatically; age-specific mortality rates at all ages declined. But there were also problems: most of the poor were not reached by Medicaid; the programs were more costly than expected, and waste, fraud and abuse by government, providers and beneficiaries seemed rampant. Government was judged to be an inefficient manager of its 40% share of national health expenditures.

The climate and the ideology began to change in the late 1970s—the right to health care was no longer axiomatic, it would have to be justified, measured, limited. Health care was no longer a public good to be made available without constraints. Health care like other goods and services would have to be rationed; choices must consider cost-effectiveness.

In 1985 a prominent Wall Street firm issued a research report modestly entitled "The Future of Health Care Delivery in America." Its major conclusions were

> The U.S. health care system is about to undergo a radical transformation. Reorganization will take the form of a wide array of economically based delivery systems that will be truly competitive and completely deregulated. As health maintenance organizations and preferred provider organizations proliferate, the current anarchic and uncontrolled fee-for-service system will be displaced by what could be called 'competitive socialized medicine,' which will control utilization, insure quality, and restrain pricing. In all this the true winner will be society, not the health industry.[2(p11)]

The societal winner in this scenario appears to be the business community. One sentence buried in the report refers to the losers: "In this system, independent and charity patients will be able to obtain care only in state, city, or county-supported hospitals."[2(p55)]

The market, and its competitive forces, is inherently inequitable and cannot be held accountable. When reliance is placed primarily on the market, and when at the same time government regulation and support is reduced, the consequences can be severe for the losers. We know that hospitals are now making record profits but are increasingly turning away the uninsured.[3] We also know that when poor people have recourse only to overcrowded and underfunded public hospitals, many have difficulty getting needed care and their health status deteriorates.[4]

In these last two decades the profession has tended to concentrate on issues of quality of care and improved technology, leaving to government and the market the assurance that standards of equity and efficiency are met. But, whether they are subject to government's inefficiencies or the inequities of a new "competitive socialized medicine," it will still be physicians who ultimately determine how this nation spends 10% of its gross national product. But if the Wall Street prognosticators are accurate, the health care market is seriously overbalancing in the direction of efficiency and cost containment at the expense of quality and access.

(Myers BA: Corporate profit or public good?—*In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Aug; 145:189-190)

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The Aim of American Medicine

The question for American medicine is with whom is it most willing to collaborate: an admittedly inefficient government or an inherently inequitable market? Under whose controls will it best be able to pursue quality and service: government socialized medicine or competitive socialized medicine?

If we continue as Wall Street predicts, the problems of the poor, of the uninsured and underserved, of a two-class health system, will become more and more apparent—even to the point of a reversal of recent positive health status trends. This will stimulate renewed discussion, by the professions and by consumers, of a national health program. Enactment of such a program that melds the capabilities and interests of the profession for quality, of the market for efficiency and of the government for equity is, it seems to me, inevitable before the end of the century. Given the experience in most other industrialized countries, it is also a desirable direction.

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The Credo of an Honored Profession

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TO DEFINE THE AIM of American medicine in today's environment, we must first know what is unique about American medicine.

When I am asked that question, it always reminds me of a story told about Benjamin Franklin. It is said that, as he left the meeting concluding the constitutional convention in 1787, a member of the waiting crowd asked him, "Mr Franklin, what kind of government have you given us—a monarchy or a federation?" He replied, "A federation, my boy, *if* you can keep it." If one were to instead ask, "What singular quality makes American medicine unique?", the paraphrased answer would be: "It is an honored profession, my boy, *if* you can keep it."

What is a profession? Traditionally, it is a field of endeavor requiring specialized knowledge obtained by prolonged and concentrated study—knowledge much beyond what the average person can be expected to obtain. Because of their acknowledged value to society, professionals are accorded certain privileges and honors, such as the privilege of self-discipline. In return, they are expected to apply this knowledge for the betterment of the greater society. In the field of medicine that professional credo can be summed up quite simply. It is "healing first and dollars second."

American medicine is currently locked in a struggle, seeking to preserve and pass on its heritage to the next generation. For the last ten years, our profession has experienced a series of hammering attacks from the "four horsemen of commercialism." They are big government, big business, the insurance complex and the hospital industry. If they had their way, the four horsemen of commercialism would change the credo of medicine from "healing first and dollars second" to "profits first and healing second."

Recently we have seen the corporate acquisition of medical schools, and a health maintenance organization in southern California advertising that its hospital will kick back a portion of profits to those doctors admitting patients with medical diagnoses that result in big profits to the hospital under the new Medicare system. I submit that professionalism itself is in an undeclared war, attacked by those committed to "bottom line" thinking.

Let me illustrate with a chilling anecdote. I recently appeared as a witness before the Prospective Payment Assessment Commission (PROPAC) in Washington, DC, along

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with several other panelists. One of the other panelists was a high official in the Health Care Financing Administration. He analyzed various ways to assess the quality of care provided under the diagnosis related group system and he warned that if mortality statistics are to be used in any comparative way, then very careful selection must be made of the right numerators and denominators in order to avoid possible distortions from extraneous factors. "Garden variety" mortality statistics would probably not be suitable (and this was his exact phrase) "if we are to obtain a picture of *the flow of death* that may, or may not, be attributable to the new payment system." The "flow of death" is a shocking phrase; it exemplifies true bureaucratic thinking, and we must never forget it.

Physicians are deeply concerned about the threat to quality in health care, but, remember, differences in that quality can only be measured in the differences in outcome experienced by a patient. There are many outcomes of importance (mortality, morbidity, patient satisfaction, lost employment and the like). When one takes all factors into account, high quality care can often be less expensive than lesser quality. When physicians speak of preserving the option of high quality care in America, *that* is what we mean.

I believe the real issue today is *not* money; that is simply the battlefield on which the real issue is being fought. It is the control of quality-of-care decision making. This control relates directly to the credo of professionalism: healing first and dollars second.

Some may ask, "Who should control quality-of-care decision making? The government, the health insurance industry or possibly the doctors?" The answer must be, "None of the above." Quality-of-care decision making should *remain* with those most closely affected by the resulting outcome, and that means patients working in concert with, and advised by, their doctors. It is a *joint* decision-making process.

Therefore, the need is for health care competition conducted in a responsible fashion, with a broader perspective than the fiscal bottom line. The phrase "caveat emptor" must never be the watchword in health.

Full-bore competition will not be painless, but competition is substantially preferable to regulation. As they say in the world of exercise and conditioning, "no pain, no gain!"

These are easily the most dynamic times ever seen for health care in this country. The generation on the firing line now must do its utmost to preserve and promote health care that is simultaneously accessible and affordable to all Americans and of the highest quality *in the judgment of those who receive it.* The success of that effort is by no means assured but, if we are to pass on "an honored profession" to those who follow, our bottom line must steadfastly adhere to "healing first and dollars second."

Clinical Investigation

Phase II Trial of β-All-*trans*-Retinoic Acid for Cervical Intraepithelial Neoplasia Delivered via a Collagen Sponge and Cervical Cap

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Retinoids are effective suppressors of the phenotypic development of cancer in many animal systems, whether the process is initiated by chemical, physical or viral carcinogens. Cases of cervical intraepithelial neoplasia are excellent for studying the effectiveness of retinoids as chemopreventive agents because the process can be closely followed by serial colposcopic and pathologic (cytology or biopsy) means and changes in the condition safely monitored. We have previously conducted a phase I study of trans*-retinoic acid (Tretinoin) given topically by a collagen sponge and cervical cap. A dose of 0.372% was selected for phase II trial. We have treated 20 patients with topical retinoic acid, and a complete response with total regression of disease was obtained in 50%. Systemic and cervical side effects were mild and vaginal side effects moderate but tolerable. These results provide a clinical basis for a randomized, double-blind phase III study to definitely answer the question of whether retinoic acid is an effective chemopreventive agent for cervical cancer.*

(Graham V, Surwit ES, Weiner S, et al: Phase II trial of β-all-*trans*-retinoic acid for cervical intraepithelial neoplasia delivered via a collagen sponge and cervical cap. West J Med 1986 Aug; 145:192-195)

Vitamin A and its natural and synthetic derivatives (retinoids) can inhibit proliferation of transformed cells in many biologic systems including murine and human melanoma, human neuroblastoma and promyelocytic cells.[1-5] They also block the phenotypic progression of preneoplastic cells to cancer both in vitro and in vivo.[6-8] In addition, clinical responses of premalignant and malignant skin and mucosal lesions to retinoids have been documented.[9-14]

To attempt to reverse established preneoplasia such as cervical dysplasia using chemoprevention is a relatively new concept. Dietary studies have also suggested that total vitamin A intake is low in patients with this disease.[15] Cervical dysplasia or cervical intraepithelial neoplasia is an ideal model for the study of chemoprevention in humans because it is a well-defined pathologic disorder that can be easily evaluated on an outpatient basis. This condition is also suitable for topical therapy, thereby possibly obviating many of the systemic side effects of the chosen intervention.

In 1981 we tested a delivery system using a collagen sponge and diaphragm, but found that patients had undesirable vulvovaginal toxicity because of leakage of retinoids around the diaphragm.[16] We next developed a new delivery device consisting of a collagen sponge and a cervical cap.[17,18] A phase I study of β-all-*trans*-retinoic acid (TRA) using the sponge and cap established that after two days evidence of effect on the cervix was present, four days of therapy was the maximum duration of treatment that most patients conveniently tolerated and side effects were tolerable with this regimen. A dose of 0.372% was determined for phase II studies.[18] The phase I study also suggested a dose-response effect, with only 2 of 14 patients responding at TRA concentrations of 0.5% to 0.116%, while 10 of 22 patients responded at concentrations of 0.158% to 0.484%. Pharmacokinetic studies using tritiated TRA have also shown rapid uptake of the retinoid into cervical tissue, with large amounts measured after four hours and nearly complete clearing by 24 hours. No

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measurable amount of retinoids was detected in serum as determined by high-pressure liquid chromatography.[19] We report here the results of a phase II trial of TRA (delivered by a collagen sponge and cervical cap device) for cervical intraepithelial neoplasia.

Patients, Materials and Methods

Patient Characteristics

For all patients in this study (in accord with a protocol approved by the University of Arizona Institutional Review Committee), a colposcopically directed biopsy specimen was used to determine if dysplasia was mild (9 patients), moderate (11 patients) or severe (5 patients). For all patients, a negative endocervical curettage and results of the pretreatment Papanicolaou smear were consistent with the ectocervical biopsy finding. The lesion and the entire transformation zone were completely visualized. The extent of the lesion was documented by colpophotographs.

TRA Administration

TRA was delivered in a cream-based vehicle that contained polyethylene 400, butylated hydroxytoluene and 55% alcohol and was a gift of G. Thorne, MD (Ortho Pharmaceuticals, Raritan, NJ). A dose of 1.0 ml 0.372% TRA was chosen based on our phase I study.[18]

The delivery system consisted of a cervical cap that was lined with a collagen sponge. The characteristics and properties of the collagen sponge and delivery system have been extensively described previously.[17-20] The cervical cap was made of the hydrogel Hypan (Sky Polymers, Princeton, NJ), which adheres to wet tissue surfaces by differential osmotic pressures. The sponges were made from pure collagen isolated from bovine skin, swollen at pH 3.0 and stabilized into the physical form of a sponge layer. Glutaraldehyde was used as a cross-linking agent to provide high resilience and fluid-binding capacity. The pore size was 400 nm (range 80 to 1,400). The sponges were cut into thin, round wafers approximately 3 to 4 mm thick and an appropriate diameter to fit the cervical caps.

One milliliter of TRA was applied to the sponge and this device was carefully inserted into the top of the vaginal vault. The position was checked to ensure placement of the cap around and against the cervix. A new collagen sponge-cervical cap device with TRA was inserted daily for four days. Patients returned at three, six and nine months for follow-up and maintenance treatment consisting of TRA at a concentration of 0.372% inserted daily for two days. The frequency and duration of maintenance treatment were selected based on the following factors: two days of treatment was the minimum time at which cervical changes were evident, retreatment for two but not for four days was acceptable to most patients, responses in the phase I trial lasted three to four months and this frequency of retreatment was deemed acceptable by most patients in a poll conducted during planning of the phase II study.

Evaluation of Efficacy and Side Effects

Patients were followed up at three-, six- and nine-month intervals with Papanicolaou smears and colposcopy. A smear having no features indicative of dysplasia or cancer cells was considered negative. At 12 months, all patients were evaluated for response with Papanicolaou smear and colposcopy. If results of either the smear or colposcopy examination were positive, ectocervical biopsy specimens were taken from the colposcopically identified lesion or the previous site of disease. The data involving the changes have been reported only for the end point of the study. The smear and biopsy results were scored blindly. Patients were considered to have a complete response if both the Papanicolaou smear and findings of colposcopy were negative or if both the Papanicolaou smear and colposcopically directed biopsies were negative 12 months after the start of treatment. At the end of the study, 15 patients had a repeat biopsy (10 nonresponders and 5 of the complete responders).

Toxicity was evaluated on days 1 through 4, day 8 and at the completion of each maintenance treatment by clinical evaluation, colposcopy and colpophotographs. Table 1 outlines the grading system for cervical and vaginal toxicity.

Results

Response to Treatment

A total of 25 patients began the phase II trial, of whom 20 were considered evaluable. Two patients were removed from the study during the induction treatment, one because of family illness and one because of inability to tolerate the cervical cap. Two patients were lost to follow-up after induction and one patient after the first maintenance treatment.

In 50% (10/20) of the patients, disease completely disappeared. Of the ten patients with a complete response, five had mild and five moderate dysplasia (Table 2). No difference in response rate was seen in patients with mild and moderate dysplasia; too few patients had severe dysplasia to evaluate. Photographs of the cervix of a patient with moderate dysplasia show the cervix before (Figure 1, left) and after (Figure 1, right) treatment.

The comparison of responders to nonresponders by the number of quadrants involved with cervical intraepithelial neoplasia, established by colposcopic examination at the beginning of treatment, is presented in Table 3. The relationship of the extent of cervical involvement to the response rate was

TABLE 1.—*Clinical and Colposcopic Grading for Cervical and Vaginal Side Effects*

Grade	*Description*
0	None
1+ (Mild)	Cervical erythema; vaginal burning, irritation, itching or discharge not bothersome to patient
2+ (Moderate)	Cervical erythema, vascularity; vaginal burning, itching or irritation bothersome to patient; erythema or increasing vascularity of vaginal mucosa, or both
3+ (Severe)	Cervical ulceration; vaginal burning, itching, irritation or discharge leading to discontinuation of treatment; ulceration or bleeding, or both

TABLE 2.—*Comparison of Grade of Dysplasia to Response*

Severity of Dysplasia	*Complete Response**
Mild	5/8 (62%)
Moderate	5/10 (50%)
Severe	0/2

*Number of patients with response versus number treated.

as follows: 100% of patients with one-quadrant disease, 50% with two- and three-quadrant disease and no patients with four-quadrant disease. In seven of the complete responders, 25% to 50% of their cervix was involved with cervical intraepithelial neoplasia, while in three patients 75% of the cervix was involved at the start of the treatments.

No patient in this series showed worsening of their dysplasia. Biopsy results in the ten nonresponders showed that five patients had improvement in the severity of their lesion whereas five patients showed no change.

Side Effects and Toxicity

The cervical side effects during the induction and maintenance treatments are summarized in Table 4. Acceptable cervical toxicity (mild to moderate) was seen in 78% of patients (18/23) during the induction treatments. Inflammation was the most frequently noted side effect, occurring in 11 patients. Increased cervical vascularity was recorded for seven patients. During maintenance treatments cervical side effects were minimal, with 9 of 50 occurrences showing mild to moderate toxicity. One patient experienced severe toxicity with cervical bleeding during the induction and first maintenance treatments.

Vaginal side effects are also summarized in Table 4. Vaginal toxicity occurred more frequently during induction as compared with the three maintenance treatments. During induction, 12 of 23 patients (52%) experienced no or mild toxicity, with increased vaginal discharge and itching occurring most frequently. During the maintenance treatments, 80% of the patients had no or mild toxicity, with increased vaginal discharge occurring most frequently. One patient experienced severe toxicity during the induction and first maintenance treatment.

The systemic side effects that occurred were very mild and included dry skin, chapped lips, decrease in appetite, change

TABLE 3.—*Comparison of Extent of Cervical Involvement to Response*

Number of Quadrants	Complete Response	No Response*
1	3	0
2	4	3
3	3	4
4	0	3
Total	10	10

*Two patients received no maintenance therapy, one patient received one maintenance dose.

TABLE 4.—*Cervical and Vaginal Side Effects*

Severity of Side Effects	Induction		Maintenance*	
	Cervical	Vaginal	Cervical	Vaginal
None	4	2	41	19
Mild	11	10	8	22
Moderate	7	10	1	9
Severe	1	1	1	1

*Total number of occurrences at three-, six- and nine-month treatments.

Figure 1.—Colposcopic view of a patient with moderate cervical dysplasia. **Left,** Day 1 before therapy. White epithelium is present on the anterior surface of the cervix with mosaicism evident from 9 to 12 o'clock. **Right,** Day 374 after induction and three maintenance treatments, three months after last treatment. A colposcopic examination shows a normal cervix.

in moods, fatigue, headaches, fever and abdominal cramping. These systemic side effects occurred more frequently during induction (9/23 patients) as compared with the three maintenance treatments (3/16 patients). Subsequent follow-up of the ten patients in complete remission a minimum of one year after the last application showed no late sequelae and nine of ten patients remained free of disease.

Discussion

The data from this study suggest that TRA suppressed cervical intraepithelial neoplasia in 50% of patients as indicated by complete regression of their disease. Whether a more intense or longer treatment would have produced a higher response rate needs to be explored and will influence, to some degree, how long these patients remain in complete response without subsequent retreatment. The severity of the dysplasia did not appear to affect the rate of response as five of eight patients with mild dysplasia and five of ten patients with moderate dysplasia had a complete response. The extent of cervical involvement with dysplasia may alter the response to topical retinoids as there was a trend towards a better response in those patients with less involvement by the cervix (Table 3). More experience will be required, however, to definitively determine whether the degree or extent of dysplasia affects response rate.

The systemic side effects seen during this phase II trial were mild and also occurred less frequently in each of the three maintenance treatments than during the induction treatments. This regression of disease was achieved with negligible cervical toxicity, as was also reported in our phase I trial.[18] Vaginal side effects, although commonly experienced during the induction treatment, were only mild to moderate and acceptable to the patients. Furthermore, during the three maintenance treatments, vaginal toxicity was seen less often and was only mild (Table 4).

The substantial suppression of cervical intraepithelial neoplasia and the absence of significant side effects during the induction and maintenance treatments provide an important basis to definitely answer whether TRA is an effective chemopreventive agent for cervical cancer. Similar conclusions have recently also been reached by Romney and colleagues who conducted a feasibility study of topical retinyl acetate administered by a vaginal applicator.[21] The eventual general clinical usage of retinoids in women of child-bearing age will need to be tempered by the knowledge that these agents[22] are potentially embryopathic and that cryosurgery and laser therapy are well proved as effective treatment for this disease. The end point of this trial and our other studies has not been to find a new treatment for cervical dysplasia. Rather, we are attempting to define the role of retinoids as an effective chemopreventive agent by reversing a preneoplastic process.

Although spontaneous regression rates for mild to moderate dysplasia may be as high as 30%, the time over which this would appear would be longer than the interval for the response seen in this study. Nevertheless, to definitely answer the question of whether TRA is an effective chemopreventive agent for cervical cancer, a phase III randomized double-blind study has been initiated to compare TRA 0.372% with a placebo cream in patients with moderate and severe dysplasia. The broad implications of a positive chemoprevention trial in this area to the field of oncology are substantial.

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Regional Air Trapping Before and After Exercise in Young Adults With Cystic Fibrosis

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Much of respiratory therapy in patients with cystic fibrosis is directed toward clearing airway secretions and dilating the airways to improve ventilation to slowly equilibrating spaces. We studied nine patients with cystic fibrosis (18 to 28 years old) who had mild to severe airway obstruction to determine whether ventilation to regions containing slow spaces was influenced by a period of exercise. Regional ventilation was assessed by measuring the trapped-air index (TAI) before and at least ½ hour after bicycle exercise. On the average, the TAI was highest in the apices and lowest in the lung bases. The apical TAI correlated significantly with the overall amount of trapped air and the forced expiratory volume in one second, indicating that abnormalities in the apices have a pronounced influence on overall lung function. For the patients with moderate or severe airway obstruction, the mean TAI decreased after exercise in the upper regions where it was abnormally high before exercise. The results suggest that slow spaces exist in the apices of all patients with cystic fibrosis who have airway obstruction and that a period of exercise improves tidal ventilation in the apices of patients with moderate or severe airway obstruction.

(Kruhlak RT, Jones RL, Brown NE: Regional air trapping before and after exercise in young adults with cystic fibrosis. West J Med 1986 Aug; 145:196-199)

Although respiratory insufficiency associated with cystic fibrosis has been extensively investigated,[1-4] there have been relatively few reports on regional lung function in this disease.[5] The respiratory component of cystic fibrosis begins with a reduced number of functional small airways, many of which through a combination of inflammation, secretions and scarring ultimately become obstructed or even obliterated.[6,7] Whether this is a diffuse process or whether some lung regions are more affected than others has not been well documented, although it has been suggested that the earliest lung function changes notable in patients with cystic fibrosis are regional inequalities of ventilation and perfusion as judged from arterial blood gas measurements.[8] Five patients studied by Tam and co-workers[5] had abnormalities of ventilation in all regions, but generally the upper regions were most abnormal.

The overall pulmonary responses during exercise in patients with cystic fibrosis have been reported,[9-13] but it is unclear how regional lung function is subsequently affected by a period of exercise. We reasoned that the increased tidal volume and higher respiratory flow rates during exercise might have therapeutic effects by dislodging airway secretions, although we recognized that the opposite might occur if airway edema or bronchospasm developed with exercise. In this study we assessed regional ventilation by measuring the rate of washout of injected saline solution of xenon 133 in patients with cystic fibrosis in whom airway obstruction ranged from slight to severe. We were interested in whether a period of exercise had any effect on the rate of ^{133}Xe washout and, by inference, regional airway resistance.

Patients and Methods

Nine patients (18 to 28 years old) with cystic fibrosis were studied while clinically stable. The diagnosis of cystic fibrosis was previously established based on clinical findings and elevated sweat chloride levels. The severity of disease was evaluated clinically and scored by the method of Shwachman and Kulczycki.[14] The patients selected had airway obstruction but none had a forced expiratory volume in one second (FEV_1) of less than 0.5 liters. Informed consent was obtained in accordance with the guidelines established by the University of Alberta Hospitals Ethical Review Committee.

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ABBREVIATIONS USED IN TEXT

FEV_1 = forced expiratory volume in one second
TAI = trapped-air index
VC = vital capacity

Overall pulmonary function measurements included FEV_1, vital capacity (VC), arterial blood gases and lung volumes by both helium dilution[15] and constant-volume whole-body plethysmography.[16]

Regional lung function was measured using ^{133}Xe and eight collinear pairs of scintillation detectors positioned so that four regions (top to bottom) of each lung were studied in the seated patients.[17] Because studies were done at two different times, the detector positions were marked on a patient's chest to facilitate realignment.

The percentage of intravenously injected ^{133}Xe remaining in each region after allowing three minutes for its washout by normal breathing of room air was defined as the trapped-air index (TAI).[18] We consider the three-minute washout period sufficient to eliminate ^{133}Xe from any reasonably well-ventilated alveoli, so an abnormally high amount of retained ^{133}Xe indicates the existence of slowly equilibrating spaces in an affected region. Therefore, the term "trapped air" is used here to describe regions with very poor ventilation or true trapped air. The TAI was calculated by dividing the regional count rate remaining in each region after three minutes of washout by the peak regional count rate after ^{133}Xe injection.[18]

Overall lung function and TAI were measured before and after a period of exercise. None of the patients had clinical, electrocardiographic or radiologic evidence of right ventricular hypertrophy. Exercise was administered by stepwise increases in workload on a bicycle ergometer (Monark). Both heart rate and ventilation rate were recorded during exercise. The ventilation rate was obtained from a dry gas meter attached to the inspiratory side of a low-resistance breathing valve. The workload was increased by 150 kpm* per minute steps until the patient reached 80% of the predicted maximum heart rate[19] or reached the predicted maximum ventilation rate ($32 + 12 \times FEV_1$),[20] whichever occurred first. This level of work was then maintained for four minutes.

*kpm stands for "kilo-pond-meter"; as a unit of power, 150 kpm per minute equals 25 watts.

Beginning a half hour after exercise when heart rate and minute ventilation had returned to preexercise levels, overall lung function and the TAI were again measured. The order of doing the postexercise studies was randomized. Measuring overall lung function required approximately 20 minutes and the TAI required approximately 15 minutes.

Lung function before and after exercise was statistically compared using the paired t test, with P values of less than .05 indicating significant differences.

Results

Table 1 shows the anthropometric data, Shwachman scores and overall pulmonary function results for the nine patients. The results indicate the presence of slight to severe airway obstruction, which caused high residual volumes and, in some patients, decreased vital capacity. The amount of air trapping, as assessed from the difference between the functional residual capacities of body plethysmography and helium dilution, was increased in all patients. Also, all patients had decreased partial pressure of arterial oxygen (normal for this age group in Edmonton is about 80 torr at a normal ventilation rate). There were no statistically significant changes in overall pulmonary function after exercise.

The distribution of the TAI is shown in Figure 1 and the individual values are listed in Table 2. There were significant increases in the TAI in the upper and middle regions while the bottom regions had a normal TAI, indicating normal ^{133}Xe washout from the lower lung regions. The exercise-induced changes in the TAI are also shown in Figure 1 and, for the nine patients, the mean TAI decreased in all regions where it was initially elevated, but none of the regions had a statistically significant fall in the TAI after exercise. There was, however, significant ($r = .81$, $P < .01$) correlation between exercise-induced changes in the TAI at the top of the lung and the FEV_1/VC ratio. Patients with a low FEV_1/VC tended to have greater decreases in the TAI, but the two patients who had an FEV_1/VC of more than 0.70 had increases in the apical TAI after exercise. When these two patients (6 and 9, Tables 1 and 2) were omitted from the analysis, we found a significant ($P < .05$) decrease in the TAI in the apices following exercise.

The mean TAI for the uppermost regions of both lungs correlated significantly with overall air trapping (Figure 2) and FEV_1 (Figure 3) in each of the nine patients studied.

TABLE 1.—*Anthropometric and Pulmonary Function Results for Nine Patients With Cystic Fibrosis*

Patient, Sex	Age, Yrs	Height, Cm	Weight, Kg	S.S.*	VC, % Pred	FEV_1, % VC	TLC, % Pred	RV, % Pred	RV/TLC	Trapped-Air Index	Pa_{O_2}, Torr	Pa_{CO_2} Torr
1 ♂	18	180	60.2	75	63	55	91	199	.45	1.33	64	30
2 ♂	18	166	52.2	86	63	56	127	380	.59	2.53	68	37
3 ♂	28	175	63.5	68	88	63	137	313	.50	2.12	65	40
4 ♂	26	183	70.6	85	86	50	149	376	.56	3.27	70	40
5 ♂	24	177	63.0	77	91	42	125	250	.43	2.17	63	39
6 ♂	20	179	50.0	69	66	70	93	192	.42	0.83	67	37
7 ♂	19	168	50.3	52	39	38	118	428	.73	3.07	59	41
8 ♀	18	169	51.8	70	77	65	130	337	.52	2.03	62	32
9 ♀	20	164	54.7	90	103	77	140	280	.40	1.12	...	...
Mean		173.4	57.4	74.7	75.1	57.3	123.3	206.1	51.1	2.05	64.8	37.0
± SD		6.8	2.4	3.9	19.4	12.8	19.9	82.6	10.5	0.84	1.3	1.4

FEV_1 = forced expiratory volume in one second, Pa_{CO_2} = partial pressure of arterial carbon dioxide, Pa_{O_2} = partial pressure of arterial oxygen, RV = residual volume, SD = standard deviation, TLC = total lung capacity, VC = vital capacity

*Shwachman Score.

Discussion

We showed that the trapped-air index is highest in the upper lung regions of patients with cystic fibrosis, suggesting that slowly equilibrating spaces are most prevalent in those areas of the lung. This pattern of regional lung function abnormality was also found by Tam and associates[5] using a different method, but the patients they studied had relatively good overall lung function. We found good correlations between the TAI in the upper regions and the indices of overall lung function (amount of trapped air and FEV_1), suggesting that much of the derangement in overall lung function in patients with cystic fibrosis is caused by the relatively poorer upper lung function.

The pattern of airway disease seen in our patients with cystie fibrosis is different from that reported for patients with

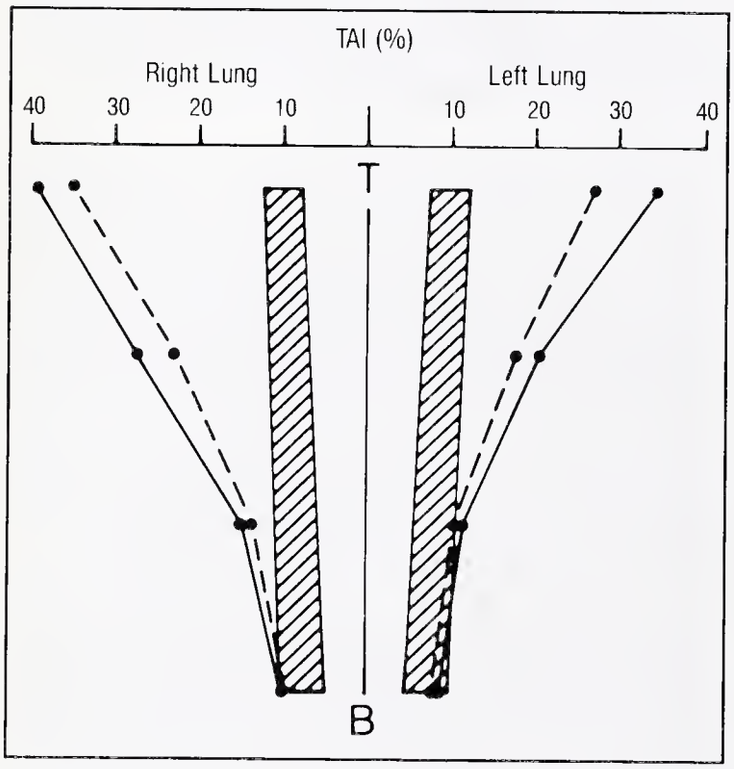

Figure 1.—The effects of exercise on the distribution of the trapped-air index (TAI) in nine patients with cystic fibrosis. The hatched areas are the TAI distributions for normal persons. The distribution of the mean TAI is shown before (solid lines) and after (dashed lines) exercise. T = top of the lung, B = bottom of the lung

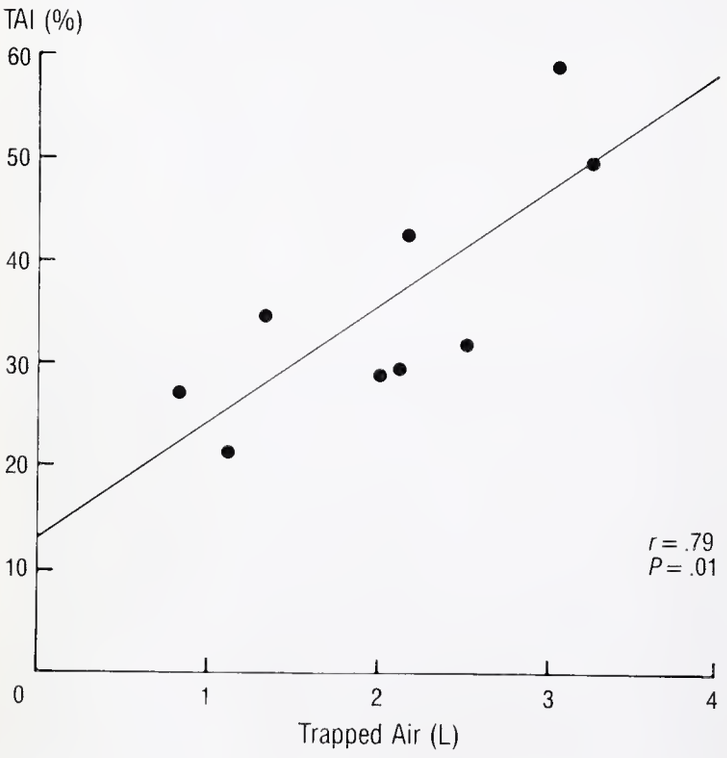

Figure 2.—Relationship between the apical trapped-air index (TAI) (mean value for the uppermost regions of both lungs for each patient) and overall trapped air as assessed from the difference between the functional residual capacity measured using the body plethysmograph and that measured using helium dilution.

TABLE 2.—*Values for the Trapped-Air Index in the Various Regions of the Lung Before and After (in Parentheses) Exercise*

Patient	*Top*	*Middle*		*Bottom*
1	34.9(32.2)	47.7(21.9)	15.4(8.0)	11.4(5.1)
2	32.1(25.9)	15.3(15.9)	12.0(14.2)	12.6(16.7)
3	29.7(30.2)	13.9(15.2)	10.0(9.8)	8.7(8.4)
4	49.8(30.7)	27.8(22.8)	8.5(12.1)	4.5(6.8)
5	42.8(37.8)	20.9(22.0)	10.9(14.5)	7.4(9.0)
6*	27.3(33.6)	13.1(14.4)	7.0(8.4)	6.3(7.8)
7	59.1(37.6)	49.9(37.3)	34.5(26.9)	23.9(18.1)
8	29.2(25.4)	17.2(11.5)	13.5(10.3)	12.4(10.4)
9*	21.4(26.2)	9.0(16.2)	4.9(7.6)	2.5(4.9)
Mean . .	36.3(31.1)	23.9(19.7)	13.0(12.4)	10.0(9.7)
±SD . .	12.0(4.7)	15.1(7.7)	8.7(6.0)	6.3(4.7)

SD = standard deviation

*Patients who had a ratio of forced expiratory volume to vital capacity of equal to or greater than 0.7.

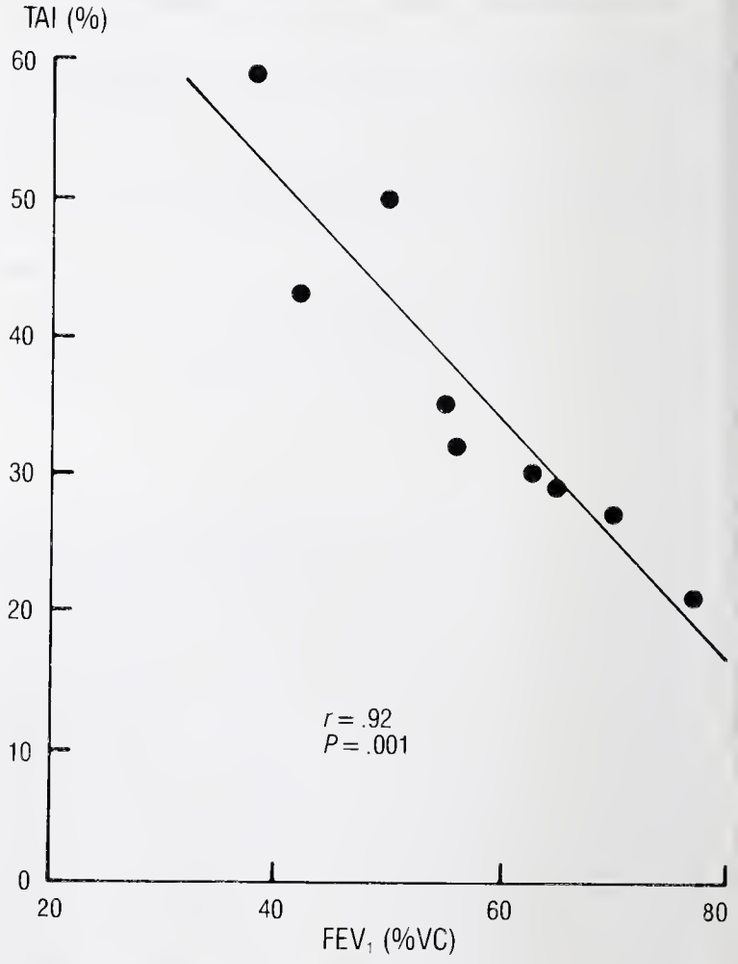

Figure 3.—Relationship between the apical trapped-air index (TAI) (mean value for the uppermost regions of both lungs) and the forced expiratory volume in one second (FEV_1) expressed as percent of vital capacity (VC).

chronic bronchitis[21,22] in whom the greatest abnormalities are typically located in the lower lung regions. The cause of these different patterns of functional impairment in patients with cystic fibrosis and chronic bronchitis is not clear, but the pattern observed in this study is consistent with the radiologic findings, which suggest that the pathologic abnormalities of cystic fibrosis are most severe in the apical regions.[23-25]

Chronic bronchitis is a product of airway irritation, so it stands to reason that the most severe disease would occur in regions receiving the greatest irritant exposure. Thus the dependent lung regions, with the highest ventilation, are the most affected.[21,22] In cases of cystic fibrosis, the hypersecretory activity[23] might be expected to cause mucus plugging in all regions of the lung and, perhaps, because of the relatively small diameter of dependent airways, one might even anticipate the greatest air trapping to occur in those regions. The TAI being highest in the nondependent regions was an unexpected finding.

It is well known that effective mucus expectoration requires a high flow velocity that in turn requires a movable air volume and high static recoil pressure in the lung segment supplying the respiratory flow. The nondependent lung regions fill relatively little, even in healthy persons,[26] during tidal breathing, and this small charge of air may be insufficient to mobilize the higher secretory volume in patients with cystic fibrosis. Also, it has been suggested that elastic recoil is decreased in these patients,[27] which, if occurring in the apices, would limit the pressure imparted to the expired gases from these regions. The end result would be a high time constant and possibly an insufficient flow velocity from the nondependent regions to dislodge the secretions, eventually resulting in mucous obliteration of some airways in the upper regions with resultant peribronchial fibrosis and airway ectasia.

The seven patients who had moderate or severe airway obstruction (as assessed from the FEV_1/VC ratio) also had a significant decrease in the TAI in the apices following exercise. Why this apparently beneficial effect of exercise was not seen in the two patients who had only slight airway obstruction is unclear. Certainly, exercise-induced bronchodilation could explain the improvement in the apical TAI, but four of the seven patients had an increased TAI in one or more regions below the apex after exercise (Table 2), suggesting that bronchodilation did not play an important part in reducing the apical TAI. In fact, one might argue that increased airway resistance developed in some of these patients with exercise and that some other effect, such as reduced mucous obliteration of airways, had the greater effect in the apices.

The two patients who had slight airway obstruction had slight increases in the TAI in all lung regions after exercise. Because one might expect secretions to be more easily dislodged in patients who can achieve higher expired flow rates, the deterioration in the TAI after exercise is interesting. Exercise-induced effects, such as bronchospasm or edema of the airway walls, may be more important than any effects of exercise that tend to improve airway function.

It was not surprising that a single period of exercise failed to improve overall lung function. Zach and colleagues[28] found that some measurements of overall lung function improved during 17 successive days of various kinds of exercise in children with cystic fibrosis. Even with these repeated exercise periods, however, the changes in lung function were small.

In summary, our results show that all patients with cystic fibrosis who have airway obstruction have slow spaces in their apices and that exercise improves the TAI in the apices of patients who have moderate or severe airway obstruction. Slight deterioration of the TAI occurs in other regions in some of these patients and patients with cystic fibrosis who have only slight airway obstruction show a generalized deterioration in their TAI after exercise. Although the mechanisms are unclear, the results suggest a combination of effects is produced by short-term exercise in these patients: one effect improves the TAI in regions where it is greatly abnormal while the other effect worsens the TAI in less abnormal regions and in all lung regions of patients with only slight airway obstruction.

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Catheter-Related Septic Central Venous Thrombosis—Current Therapeutic Options

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Central venous catheter-related infection and evidence for central venous thrombosis developed in five patients. On the basis of ongoing bacteremia after catheter removal and venographic confirmation, catheter-related septic central venous thrombosis (CR-SCVT) was confirmed. These patients were treated successfully with anticoagulation and antibiotics; none required surgical exploration or drainage.

CR-SCVT is a complication of modern venous access techniques and is easily confused with sepsis from other anatomic sites. Even when recognized antemortem, CR-SCVT carries an excessive morbidity and mortality. The therapy for this complication is not standardized, but catheter removal, anticoagulation and a prolonged course of antibiotics are appropriate initial therapy. Surgical vein ligation or excision are reserved for refractory sepsis or abscess formation.

(Kaufman J, Demas C, Stark K, et al: Catheter-related septic central venous thrombosis—Current therapeutic options. West J Med 1986 Aug; 145:200-203)

As complications of modern central venous access techniques, central venous thrombosis and catheter-related sepsis are individually well recognized.[1-5] The simultaneous occurrence of these two complications, catheter-related septic central venous thrombosis (CR-SCVT) is remarkably uncommon, with few well-documented cases in the literature and serious associated morbidity and mortality. Over a two-year period, we have treated five patients with proved CR-SCVT. In the present report we describe the peculiar problems associated with the diagnosis and treatment of this unusual disease.

Clinical Material

CR-SCVT is defined as the simultaneous occurrence of three findings: venographically proved thrombosis of the internal jugular, subclavian or brachiocephalic veins; central venous catheter infection, defined by positive catheter tip and peripheral blood cultures; ongoing bacteremia after catheter removal.[6]

Five patients considered to have CR-SCVT were treated by us between September 1983 and September 1985. Their clinical summaries are presented in Table 1. Catheter infection became evident 13.4 days after placement (mean; range 6 to 30 days). All patients had fever and leukocytosis. Signs of sepsis were described as moderate to severe in three patients, with tachycardia, mild hypotension and cardiac rhythm disturbances. Local signs of venous thrombosis (aspiration of thrombus from the catheter; ipsilateral neck, chest wall or upper extremity edema) were present in all cases, as was venographic confirmation of thrombosis. Cultures of peripheral blood and catheter tips yielded *Staphylococcus aureus* in all cases, and bacteremia continued after the catheter was removed. Endocarditis was excluded in all patients, based on the absence of new cardiac murmurs, the absence of evidence for peripheral microembolization or vasculitis and normal echocardiography.

Radiographic Signs

Venograms were abnormal in all instances, four with total venous thrombosis and one with a large nonocclusive mural thrombus in the subclavian vein (Figures 1 through 4). A perivenous phlegmon was shown by computed tomography at the level of thrombosis in two patients, one of whom also had mediastinal widening on a standard chest radiograph.

Treatment and Response

All patients received antibiotics intravenously and anticoagulation. Continuous heparin infusion was administered

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ABBREVIATIONS USED IN TEXT

CR-SCVT = catheter-related septic central venous thrombosis
CT = computed tomography
MLC = multiple-lumen [central venous] catheter

in a dosage sufficient to maintain the partial thromboplastin time twice control. Anticoagulation was continued for ten days in four cases, a time period during which there was clinical or radiographic evidence for cessation of active thrombosis. Nonocclusive thrombosis was present in one patient (case 3) with Wegener granulomatosis, renal failure and hemoptysis, an absolute contraindication to full continuous anticoagulation. He received thrice-a-week systemic anticoagulation with heparin during hemodialysis. All patients sur-

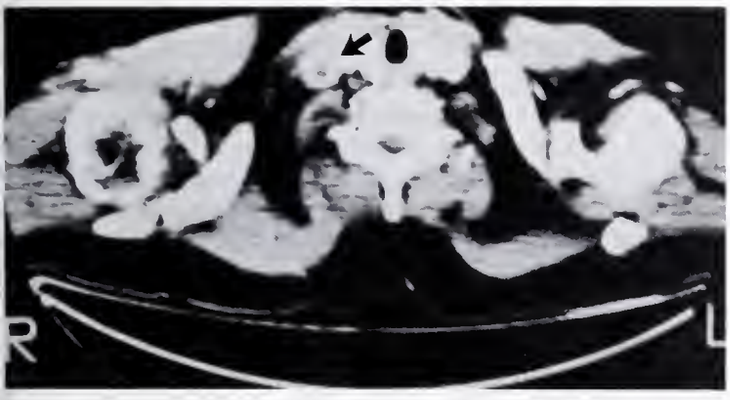

Figure 1.—An intraluminal thrombus in case 1: Computed tomography of the upper mediastinum, with radiographic contrast, shows thrombus **(arrow)** in the right internal jugular-brachiocephalic vein segment.

Figure 2.—Total venous occlusion in case 2: A digital subtraction venogram shows left subclavian, jugular and brachiocephalic venous occlusion.

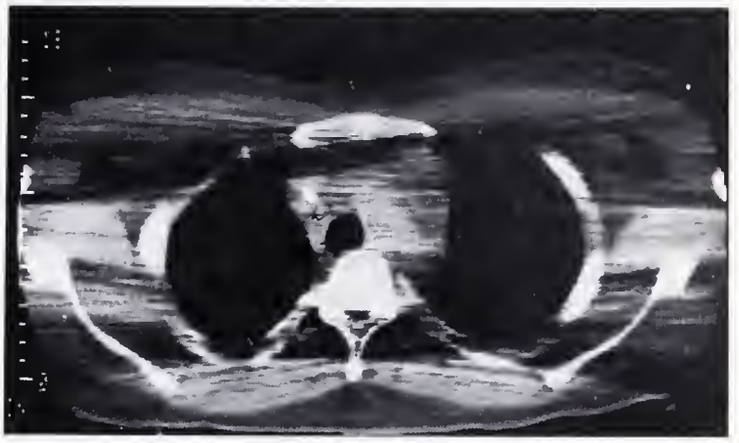

Figure 3.—A mediastinal phlegmon in case 2: Computed tomography of the upper mediastinum shows the mediastinal widening and effacement of structural borders typical of a mediastinal phlegmon from catheter-related septic central venous thrombosis. The arrow marks the position of a right internal jugular central venous catheter. Bony artifact is present.

Figure 4.—A sleeve thrombus in case 3: A right upper extremity venogram shows a sleeve thrombus **(arrow)** at the junction of the subclavian and internal jugular veins.

TABLE 1.—*Confirmed Cases of Catheter-Related Septic Central Venous Thrombosis—Present Series*

Patient	*Age*	*Sex*	*Underlying Disease*	*Type of Catheter*	*Interval: Placement to Infection, Days*
1	72	F	Pancreatitis	Pulmonary artery, introducer sheath, internal jugular	6
2	26	M	Testicular carcinoma	Hickman Silastic subclavian	30
3	34	M	Wegener granulomatosis	Subclavian dialysis catheter	14
4	20	M	Multiple trauma	Single lumen subclavian	11
5	34	F	AIDS	Multiple-lumen internal jugular	6

AIDS = acquired immunodeficiency syndrome

vived without residual symptoms of thrombosis. Although pulmonary angiograms or lung scans were not done, there was no clinical evidence of pulmonary embolism in any patient. After the acute thrombosis resolved, there were no late sequelae due to venous hypertension in any patient.

Antistaphylococcal agents were selected on the basis of sensitivity testing and were administered for four to six weeks. In case 1, a two-week course of nafcillin given without anticoagulation was followed by recurrent bacteremia and clinically active thrombosis with tenderness, erythema and edema in the neck ipsilateral to the site of catheterization. Although antibiotic therapy was restarted at the recurrence of fever, it was only after the addition of heparin that the process abated.

Discussion

Strictly defined, CR-SCVT is proved thrombosis of the jugular, subclavian or innominate veins, catheter infection and continued bacteremia after catheter removal.[6] CR-SCVT must be differentiated from simple catheter contamination without thrombosis, exit-site sepsis, skin tunnel infection and infusion fluid sepsis. In an exhaustive analysis of reported catheter complications, including all types of central venous catheters currently available, we have been able to find only 32 confirmed and 5 probable cases of CR-SCVT diagnosed antemortem.[1-3,6-13]

The rarity of CR-SCVT is difficult to explain, in view of the relatively common occurrence of catheter sepsis and central venous thrombosis alone. Some of the recent developments in catheter technology, such as reductions in thrombogenicity with polyurethane construction or heparin bonding,[6,14] may reduce the possibility of CR-SCVT, but these precautions are clearly imperfect. Catheter-related thrombosis has an incidence ranging from 8% to 90%,[2,15-18] depending on the type of catheter used, its location and duration of placement. Despite careful nursing care, sepsis occurs in 3% to 21% of catheters.[4,5,19] In reviewing the present cases, there were no apparent errors in catheter management to account for the rapid case accession, which appeared related to an intensive search for CR-SCVT. Therefore, it seems that CR-SCVT has been underdiagnosed in other analyses of catheter-related complications, in particular because of the ease with which CR-SCVT may be overlooked in the presence of concurrent sources of sepsis or multisystem organ failure.

CR-SCVT occurred during the use of a wide variety of catheters. The association with Silastic Hickman catheters (case 2) has been described previously.[6] The associations with a subclavian dialysis catheter, a pulmonary artery catheter introducer sheath and a multiple-lumen central venous catheter (MLC) have not been previously described, and each catheter has peculiar risk factors for CR-SCVT. Introducer sheaths[20] are often left in place for long periods and, due to their bulkiness and the presence of a side-arm infusion port, are difficult to maintain with sterile dressings. They have rubber diaphragm partition mechanisms that may fail, allowing bacterial entry. Because early formation of a fibrin sheath around pulmonary artery catheters is well defined,[14] sheath thrombosis may be common, but no study has examined its incidence. Subclavian dialysis catheters are likewise stiff and difficult to maintain with a sterile technique when used in an outpatient setting.[21] Sepsis has been reported in as many as 14% of these catheters[22,23] and thrombosis in at least 2%.[21-23] CR-SCVT was not a complication in the one MLC series reported to date.[24] The risk faetors for CR-SCVT in association with MLC include use in an intensive care unit, the wide variety of infusions administered and the duration of catheterization.[12]

A suspicion of CR-SCVT necessitates a departure from the ordinary management of catheter sepsis. Because the treatment of CR-SCVT is prolonged and costly, it should be differentiated carefully from the other sources of sepsis that may be present in this seriously ill population. The most prominent diagnostic feature is continued bacteremia after catheter removal. Venography, which may be done at the bedside, is necessary to confirm thrombosis. Cases 2 and 3 show the possible variation in the pattern of thrombosis, from a large sleeve thrombus to a mediastinal phlegmon about a totally thrombosed vein. Echocardiography is used to exclude a valvular lesion from endocarditis, which may be induced by long catheters on the tricuspid or pulmonary valves.[25] Computed tomography (CT) is a useful adjunct to define regions of thrombosis and to observe the resolution of assoeiated inflammation.[10,26] CT is diagnostic for the development of an abscess in an area of mediastinal phlegmon.

Treatment of CR-SCVT is not standardized, in contrast to the generally accepted use of excision and antibiotics in the treatment of septic venous thrombosis at peripheral catheter sites.[27,28] If the pelvic veins and the inferior vena eava are included in review, central venous septic thrombosis has a long history of evolving treatment. Trendelenburg first described the use of vein ligation in 1906.[29] In 1947 Neuhof and Seley noted the effectiveness of local phlegmon drainage and antibiotics.[30] Mitre and Rotheran later described the added need for anticoagulation to achieve control of eentral septic venous thrombosis.[31] More recent attention has returned to the use of vein ligation, excision or thrombectomy as the primary treatment.[7] Only 13 of the 37 case reports of CR-SCVT noted above included a description of the treatment: five with antibiotics alone, six with anticoagulation and antibiotics and two with ligation or thrombectomy. The outcome among 22 determinant cases was 14 survivors (63%) and 8 fatalities (37%). There was no correlation between a particular treatment and survival. Notably, septic pulmonary embolization occurred in 4 of 16 patients (25%) for whom complications were described.

Based on the present experience, it appears that removing the inciting catheter, intravenous administration of antibiotics and anticoagulation are appropriate initial therapy. Heparin is important in halting the extension of septic thrombus and in preventing pulmonary embolization, which has been reported in as many as 32% of patients with central venous thrombosis.[1] Heparin should be given at full doses for a period long enough to achieve clinical resolution of the thrombotic process.[32] In the four cases in which thrombosis was associated with clinical signs, this resolution occurred over a one-week period. The choice of antibiotics is based on specific organism sensitivity testing. Because the organizing thrombus may be a privileged endovascular site with potentially reduced drug levels,[12] antibiotics should be administered in a quantity and for a duration similar to those for endocarditis. Insufficient antibiotic therapy may lead to recurrent bacter-

emia, as occurred in case 1. Surgical therapy is indicated after failure of an adequate course of antibiotics and anticoagulation. The presence of a phlegmon alone at the site of thrombosis is not an indication for exploration. Drainage is indicated after clinically unmistakable mediastinal abscess develops. Ligation and transcervical or transthoracic excision of central veins should be only rarely indicated, primarily in the presence of recurrent bacteremia and when a phlegmon fails to resolve.[7]

Catheter-related central septic venous thrombosis is a disorder that deserves increased attention in the modern era of invasive monitoring and intravenous therapy. Any patient with a catheter-related infection and persistent bacteremia after catheter removal should receive a full evaluation for CR-SCVT, including venography. If CR-SCVT is defined, anticoagulation and a prolonged course of antibiotics given intravenously are the preferred initial treatment.

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Amatoxin Poisoning in Northern California, 1982-1983

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Twenty-two patients who ate mushrooms containing hepatotoxic amatoxins were treated during the fall and winter seasons of 1982 and 1983. All patients were treated with intensive supportive care and repeated oral doses of activated charcoal. In two patients fulminant hepatic failure developed and they died. One patient in whom encephalopathy developed had an orthotopic liver transplant and survived. Liver biopsy specimens obtained from five patients during the acute illness showed centrilobular hemorrhagic necrosis. The hepatic histopathology in a biopsy specimen from a 5-year-old boy eight weeks after mushrooms were eaten showed bands of fibrosis and islands of hepatocytes suggestive of early cirrhosis. Radioimmunoassay for amanitins, done on the serum from all patients, detected the toxins in only three, probably because most of the specimens were obtained 24 hours or more after the ingestion. This series, with a mortality rate of 9%, illustrates the outcome in patients who receive intensive supportive care and provides a background on which success of specific treatments should be judged.

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As interest in collecting and consuming wild mushrooms has grown in the United States over the past few years, a greater number of amatoxin-poisoned patients has been reported, particularly from the West Coast.[1-4] The management of toxicity remains a difficult clinical problem. There is no specific treatment and therapy has been largely empirical. In 1982 we reported the cases of ten patients and reviewed in some detail clinical features, diagnosis, treatment and identification of the amatoxin-containing mushroom species.[5] During the fall and winter seasons of 1982 and 1983, we treated 22 more patients who form the basis of this report.

Reports of Cases

The clinical and laboratory data (initial, peak and convalescent values) from the 22 patients are summarized in Table 1. Thus, only a brief history of each patient or groups of patients will be given. All patients were treated with repeated doses of activated charcoal given by mouth (15 to 30 grams every four to six hours) for 48 to 72 hours. Patients 1, 2, 13, 14 and 15 were given a single dose of dexamethasone intravenously (4 to 8 mg) on admission.

Case 1

The patient, a 23-year-old 70-kg (154-lb) logger was well until the end of November 1982 when he picked and ate several mushrooms. Six hours later bouts of severe crampy abdominal pain, watery diarrhea, nausea and vomiting developed. When he presented to a community medieal center about 14 hours after the ingestion, he had right upper quadrant tenderness and was dehydrated. The hematocrit was 55%. He was transferred to the San Francisco General Hospital Medical Center on the second hospital day beeause of worsening abdominal pain and high serum aminotransferase activity.

On examination, the patient was afebrile and, apart from abdominal tenderness, the physical examination showed no abnormalities. A regimen of repeated oral doses of activated charcoal (17 grams every four hours) was begun. Over the next four days, hepatic failure and eneephalopathy developed. By day 7, the patient was obtunded and a duodenal tube was inserted. Charcoal hemoperfusion across a Gambro Adsorba 300 C cartridge (Gambro, Inc, Newport News, Va) at a blood flow rate of 250 ml per minute via two No. 7 French

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femoral venous catheters was carried out daily for six hours on three consecutive days. His condition continued to deteriorate and an intractable lactic acidosis developed. He underwent a three-hour porcine liver perfusion on the seventh day but adult respiratory distress syndrome, septicemia and irreversible shock developed and he died on the ninth day after ingestion.

On postmortem examination there was moderate cerebral

TABLE 1.—*Pertinent Data in 22 Cases of Amatoxin-Containing Mushroom Poisoning*

Case	Age, yr	Sex	Symptoms	Onset, h	Days After Ingestion	AST,* units/liter	ALT,† units/liter	Total Bilirubin,‡ mg/dl	Prothrombin Time,§ sec
Fatal Cases									
1	23	M	Nausea, vomiting, abd cramps, WD	6	1	...	91	...	13.5
					3	1,760	6,260	2.4	47.9
					8	1,005	810	11.0	107.8
2	35	M	Nausea,vomiting, abd cramps,WD	6	1	1,820	...	...	13.0
					4	2,720	6,620	5.3	62.5
					8	70	890	13.8	21.9
					14	62	94	18.9	24.0
Survivors									
3	3	F	Nausea, vomiting, abd cramps, WD	8	3	16,626	9,841	2.3	...
					5	10,405	5,965	4.4	49.8
4	22	F	Nausea, vomiting, abd cramps, diarrhea	8	1	874	613	...	22.6
					3	11,674	9,233	3.0	28.2
					5	3,277	5,587	7.1	24.4
					12	42	...	7.9	16.8
5	5	M	Nausea, vomiting, abd cramps, WD	8	1	2,260	2,560	...	14.9
					3	2,771	3,488	0.8	12.6
					5	129	861	0.6	10.6
6	82	F	Nausea, vomiting, diarrhea	14	3	740	285	1.7	13.2
					4	2,070	2,160	1.2	15.4
7	54	F	Nausea, vomiting, diarrhea	7	2	38	72	1.2	11.5
					3	29	50	0.6	11.7
8	30	F	Nausea, vomiting, abd cramps, WD	12	12	56	40	...	10.0
9	21	F	Nausea, vomiting, abd cramps, WD	12	3	71	75	...	15.8
					4	2,580	2,530	3.6	25.2
					8	172	591	9.1	13.0
10	23	M	Nausea, vomiting, abd cramps, WD	12	2	153	224	0.5	11.5
					4	1,565	3,690	1.1	11.6
					7	50	955	0.4	10.4
11	30	F	Vomiting, abd cramps, diarrhea	6	2	33	...	0.6	12.5
					5	1,720	...	1.6	16.5
					7	775	...	1.2	13.4
12	49	F	Vomiting, abd cramps, diarrhea	29	2	20	...	0.6	11.0
					6	77	...	1.2	11.2
13	35	M	Vomiting, abd cramps, diarrhea	6	2	230	...	0.8	13.2
					4	7,880	...	3.8	34.0
					6	1,980	...	8.0	60.4
					20	65	...	13.0	12.1
14	66	M	Vomiting, abd cramps, diarrhea	6	2	254	...	1.0	11.4
					4	2,760	...	5.6	20.5
					7	475	...	8.8	13.8
					16	55	...	1.8	10.8
15	30	F	Vomiting, abd cramps, diarrhea	24	2	312	...	1.0	12.3
					5	1,880	...	2.3	12.4
					8	48	...	1.0	10.6
16	36	M	Abd cramps,diarrhea	27	2	222	...	0.5	11.2
					8	87	...	0.6	11.0
17	14	F	Vomiting, abd cramps,diarrhea	29	3	57	...	1.2	10.8
					7	55	...	2.0	10.9
18	28	F	Nausea, vomiting, diarrhea	12	4	28	...	1.2	14.0
19	31	F	Nausea, vomiting, diarrhea	12	4	15	...	0.9	11.0
20	8	M	Vomiting, abd cramps, diarrhea	12	4	1,115	1,180	0.03	13.4
					5	248	148	0.5	...
21	9	M	Vomiting, abd cramps, diarrhea	12	1	820	730	0.4	12.9
					5	180	439	0.7	...
22	7	M	Nausea	12	3	25	...	...	12.6

Abd = abdominal, ALT = alanine aminotransferase, AST = aspartate aminotransferase, WD = watery diarrhea

*Normal < 35 units/liter.
†Normal < 45 units/liter.
‡Normal 0.5 to 1.5 mg/dl.
§Normal 10 to 12 sec.

edema, aeute pulmonary congestion and focal edema. Microscopie examination of the liver showed massive centrilobular necrosis with viable hepatocytes near portal triads and mild steatosis (Figure 1).

Case 2

The patient, a 35-year-old 85-kg (187-lb) man who picked and ate the mushrooms with patient 1, presented with the same clinical manifestations and was treated similarly until the sixth day when encephalopathy developed. In the intensive eare unit he was hemoperfused daily for eight days and had a 1½-hour poreine liver perfusion on day 7. His intracranial pressure was normal until the eighth day when administration of mannitol was required. Also on the eighth day generalized seizures developed and a continuous infusion of pentobarbital for 48 hours was begun. On day 12, the pentobarbital concentrations in the blood had been reduced to zero by repeated hemoperfusions. Studies of brain electrical activity, including an electroencephalogram and brain-stem evoked potential, indicated electrical silenee. Ventilatory support was withdrawn on day 13, following which the patient died rapidly.

On postmortem examination there was eerebral swelling, edema, compression of the posterior cerebral arteries and subsequent hemorrhagic infarction of the temporal lobes. Microscopic examination of the liver showed mild steatosis and pronounced centrilobular neerosis characterized by disappearance of hepatic cells and replacement by an eosinophilic mesh. The areas of neerosis were infiltrated by a mononuclear, predominantly lymphocytic, cell infiltrate. The portal traets were relatively uninvolved. There was no increase in fibrous connective tissue and no evidenee of collapse of the reticular structure. The lungs showed bronchopneumonia. All other organs were normal.

In both cases 1 and 2, the uneaten mushrooms were identified by a member of the San Francisco Mycological Association as *Amanita phalloides* species by visual inspection and a positive Meixner test.[6] Serum specimens taken from patient 1 at 24 hours and from patient 2 at 12 hours postingestion had amanitins detected by radioimmunoassay,[7] although concentrations were too low to be measured aecurately. Urine and gastric aspirate collected from each patient on the second day after ingestion did not have detectable quantities of amatoxins.

Case 3

This patient, a 3-year-old girl (13.2 kg [29 lb]) whose full clinieal course has been reported elsewhere,[8] ate mushrooms late in February 1983 and eight hours later nausea, vomiting, abdominal cramps and watery diarrhea developed. She was admitted to a community hospital and the San Francisco Bay Area Regional Poison Control Center was consulted. She was rehydrated and oral doses of activated charcoal were begun. On the third day, she was transferred to the University of California Davis Medieal Center because of worsening results of liver function tests and encephalopathy. Pneumococcal septicemia, acute renal failure and intractable hypotension developed and she required assisted ventilation. On the sixth day postingestion, an orthotopic liver transplantation was carried out. Microscopic examination of the liver (Figure 2) showed a virtual lack of intact parenchymal cells and hemorrhagie necrosis. The patient was maintained on a regimen of cyclosporin and eorticosteroids in varying doses to control rejection for the remainder of her hospital stay. Now her liver function is normal but she has residual neurologic deficits.

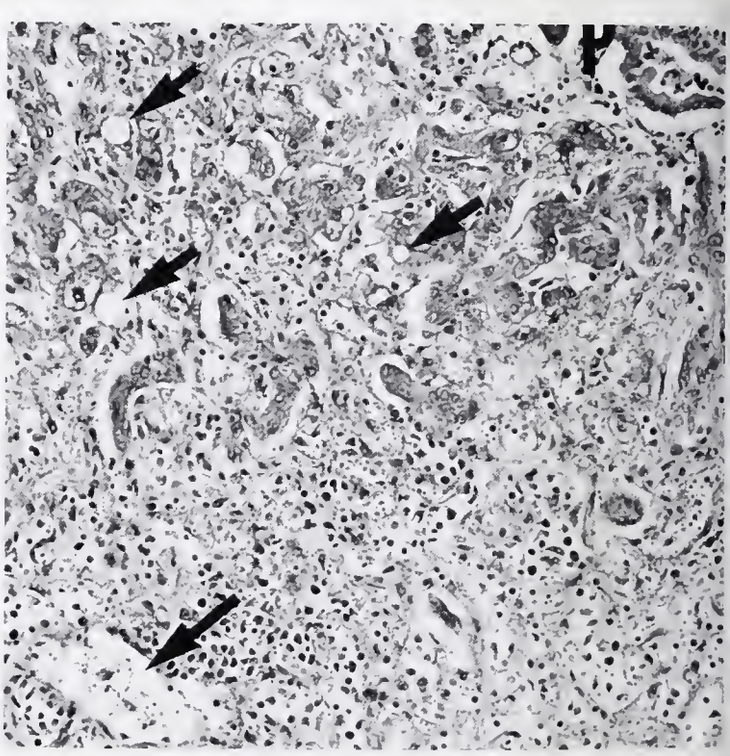

Figure 1.—Photomicrograph of a section of liver obtained at autopsy from the patient in case 1. There is a zone of necrosis surrounding a central vein **(long arrow)** with viable parenchymal cells near the portal triad **(P)**. Mild steatosis **(short arrows)** is also present (hematoxylin-eosin stain, magnification × 74). Clinton Teague, MD, prepared photomicrograph and interpreted the histopathology.

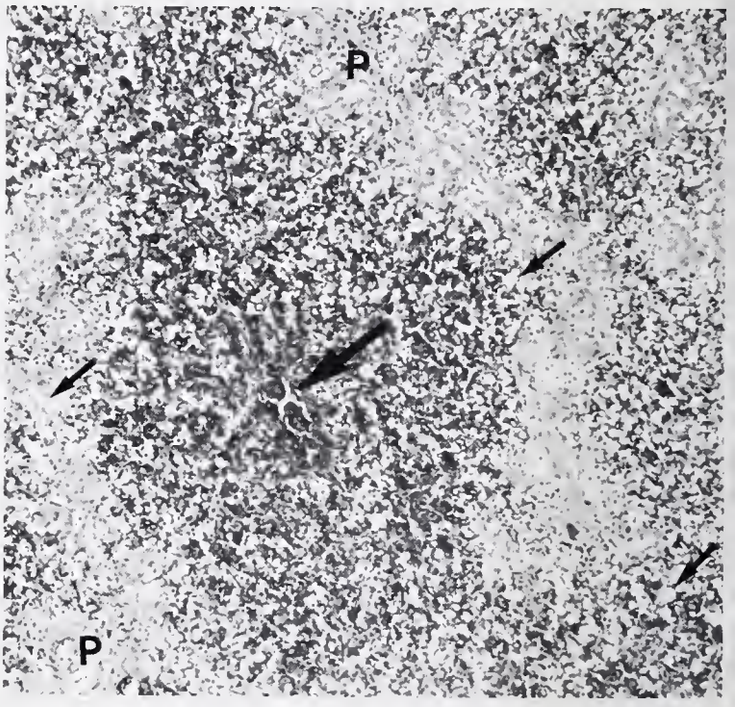

Figure 2.—Photomicrograph of a section of the liver removed from patient in case 3. There is massive hemorrhagic parenchymal cell necrosis extending from the central vein **(large arrow)** and leaving only a narrow rim of hepatocytes adjacent to portal areas **(P)**. Prominent steatosis is also present **(small arrows)** (hematoxylin-eosin stain, magnification × 74). Clinton Teague, MD, prepared the photomicrograph and interpreted the histopathology.

A serum specimen obtained 72 hours after ingestion did not contain detectable amanitins, nor did a homogenate of the patient's liver.

Cases 4 and 5

Patient 4, 22 years old, is the mother of patients 3 and 5. She and her children became symptomatic about eight hours after eating mushrooms picked in a field in the Fresno area of California. Encephalopathy did not develop in patient 4 and she recovered fully without any complications.

Patient 5, age 5 years (16.5 kg [36 lb]), received lactulose for mild encephalopathy that developed on the fourth day. Glucose intolerance also developed and he had a Fanconi-type of renal tubular dysfunction, both of which gradually resolved. He was discharged on the 18th day after ingestion. Eight weeks after the original admission to hospital, he returned for a liver biopsy. On microscopic examination (Figure 3), there were irregular islands of hepatocytes separated by bands of fibrous tissue. No active inflammation was evident.

A serum specimen obtained from this patient 24 hours after the ingestion contained detectable amanitins but not in a concentration sufficient to be quantitated. A serum specimen from patient 4 obtained at the same time had no detectable amanitins.

Uneaten mushrooms involved in cases 3, 4 and 5 were identified by a mycologist as *Amanita ocreata*.

Cases 6 and 7

Two Filipino women, mother and daughter, aged 82 and 54, respectively, shared two cooked mushrooms in March 1983. In both women nausea, vomiting and bloody diarrhea developed 14 and 7 hours, respectively, after the ingestion. They were admitted to the hospital the following day because of continuing gastrointestinal symptoms. Neither patient had hepatic encephalopathy and both were discharged within a week of the ingestion.

No biologic specimens were obtained for determination of amanitins. Uneaten mushrooms in the house were identified as *A ocreata*.

Case 8

The patient, a 30-year-old woman, ate a 2.5-inch mushroom cap at 5 PM in October 1983. She awoke 12 hours later with abdominal cramping, repeated vomiting and diarrhea for which she received thorazine in an emergency department and was rehydrated. She was transferred to the San Francisco General Hospital Medical Center for further care, which consisted of further rehydration and insertion of a duodenal tube to administer activated charcoal for 48 hours. Mild right upper quadrant tenderness developed but the patient had no other symptoms or signs of hepatic injury.

A watery stool specimen obtained 24 hours postingestion contained 76 ng per ml of amatoxin. Mushrooms she had picked were examined by a mycologist who identified two amatoxin-containing mushrooms, *A phalloides* and *Lepiota clypeolaria*. The Meixner test[6] and the radioimmunoassay[7] on a methanolic extract of the cap was positive in a mushroom similar to the one the patient said she ate. This had the characteristics of *A phalloides*.

Cases 9 to 22

In December 1983 a Laotian man collected in the Napa Valley and shared with 14 people mushrooms that fitted the description of *A phalloides*. Vomiting and diarrhea developed in all 14 within 6 to 12 hours and they were admitted to several hospitals in the Bay Area.

Patients 9 and 10 were admitted to the San Francisco General Hospital Medical Center. Patient 9, a 21-year-old woman, was rehydrated and a course of activated charcoal was begun. Her prothrombin time and serum aminotransferase activity increased but neither encephalopathy nor overt bleeding developed. She was discharged on day 9 with normal results on liver function tests.

Patient 10, a 23-year-old Laotian man, had the same symptoms and clinical course as patient 9, except that he had fever (39°C [102°F]) for the first four days. On the seventh day postingestion a percutaneous liver biopsy specimen showed prominent centrilobular necrosis and hemorrhage.

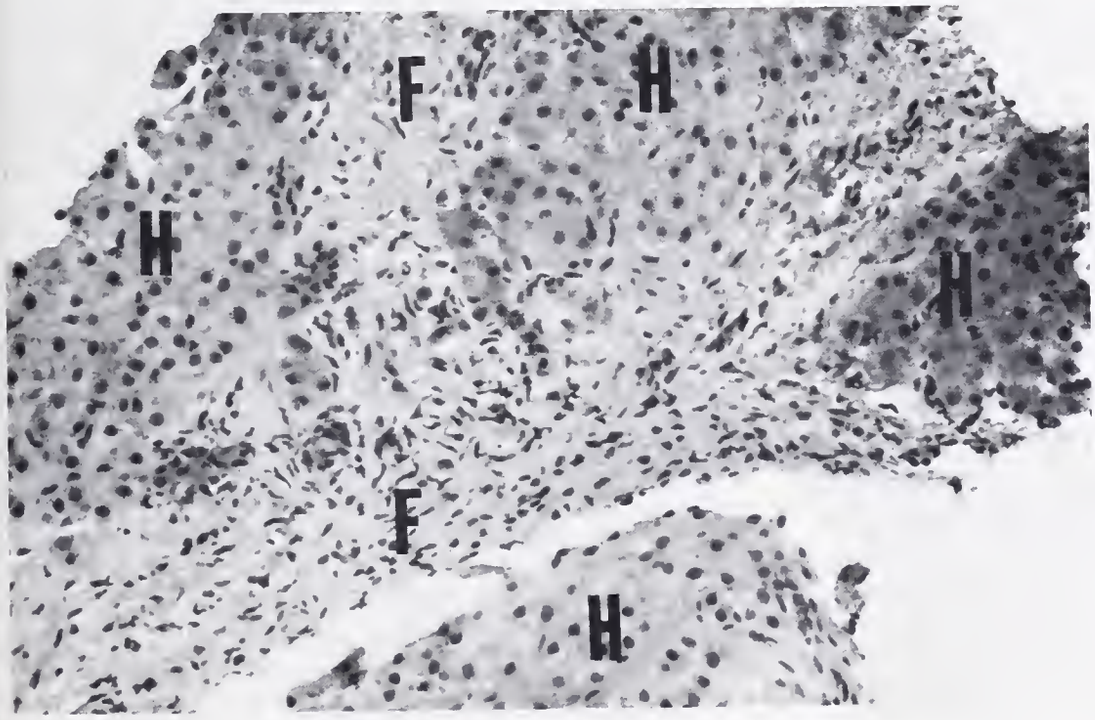

Figure 3.—Photomicrograph of a section of liver obtained from patient 5 by percutaneous biopsy eight weeks after the ingestion of *Amanita ocreata*. The fragmented specimen shows irregular islands of hepatocytes **(H)** lacking normal lobular architecture and separated by bands of fibrous tissue **(F)** (hematoxylin-eosin stain, magnification × 290). Clinton Teague, MD, prepared the photomicrograph and interpreted the histopathology.

Binucleate hepatocytes and mitotic figures were present in nonnecrotic areas.

Patients 11 through 17 were admitted to Brookside Hospital in San Pablo, California. In four of these patients, clinical evidence of hepatic injury developed.

In patient 13, a 35-year-old man, severe abdominal cramps, vomiting and profuse watery diarrhea developed six hours after he consumed half a bowl of a mushroom stew. He presented on day 2 of the illness, was rehydrated and given activated charcoal orally. Blood cultures on day 6 grew *Streptococcus pneumoniae* and *Hemophilus influenzae*, and ampicillin therapy was begun. A spontaneous hematoma of the thigh developed on day 9. At this time the prothrombin time was 27 seconds (control 13), the partial thromboplastin time 97 seconds (normal less than 40), the serum fibrinogen level 55 mg per dl (normal 170 to 410) and the platelet count 88,000 per μl. His serum ammonia concentration reached a maximum of 175 mg per dl on day 5. No signs of hepatic encephalopathy developed and he was discharged on day 21.

Patient 14, the 66-year-old father of patient 13, was severely dehydrated and oliguric on admission, 24 hours after ingestion. His blood pressure was 130/70 mm of mercury, his heart rate 108 beats per minute and he had an arterial blood pH of 7.15 and a partial carbon dioxide pressure of 24 torr. The blood urea nitrogen and creatinine levels were 48 and 3.5 mg per dl, respectively. The pulmonary capillary wedge pressure was less than 3 mm of mercury. After aggressive fluid and bicarbonate replacement, his blood pressure and urine output stabilized and the blood urea nitrogen and creatinine levels decreased to 34 and 2.3 mg per dl, respectively. The maximum prothrombin time was 20.5 seconds and the serum ammonia level was 113 mg per dl. He recovered uneventfully and was discharged on day 16.

Patients 11, 12, 16 and 17 had mild alterations in liver function test results and uneventful clinical courses.

In patient 15, rhabdomyolysis and substantial muscle weakness developed that were maximal on day 7. The serum creatine kinase level reached its peak (2,875 units per liter, normal 21 to 215) on day 7. In addition, the MB bands were positive, although the electrocardiogram remained normal.

Patients 12 and 17 had mild nausea, vomiting, diarrhea, minimal elevation of serum aminotransferase values and uneventful clinical courses.

Patients 18 and 19 had minimal symptoms and normal liver function tests.

Patients 20 to 22 were children aged 8, 9 and 7 years, respectively. All had mild symptoms. Two had slightly abnormal liver function tests and all recovered rapidly.

No amanitins were detected in serum or urine specimens collected 24 hours after ingestion in any of patients 9 through 22. No mushrooms were available for identification in these cases.

Discussion

A characteristic feature of amatoxin poisoning is the latent period of 6 to 12 hours during which the victim is asymptomatic. The first (gastrointestinal) phase begins with symptoms of severe abdominal cramping, vomiting and profuse watery diarrhea, often described as "rice water" or "choleralike." Profound dehydration and circulatory collapse may result. Often these symptoms remit considerably after 24 hours and the patient may appear to improve. During this second phase of apparent recovery, elevation of serum aminotransferase levels and prothrombin time may become evident along with hypoglycemia, all due to hepatic injury. In the third phase, hepatic and renal injury become clinically apparent and may progress to fulminant hepatic failure. Mortality in patients in whom encephalopathy develops is very high.[5] In some patients, however, the mortality also appears to be correlated with the severity of the gastroenteritis and the degree of the dehydration.[5]

Amanita phalloides mushrooms and similar species contain two principal groups of toxins: amatoxins and phallotoxins. The phallotoxins, which are poorly absorbed from the gastrointestinal tract, do not contribute to hepatic manifestations of *A phalloides*-type poisoning in humans.[9,10] The amatoxins consist of at least five cyclic octapeptides, the major ones being α- and β-amanitin (molecular weight about 500 daltons), which differ only slightly in structure. A single mushroom can contain a dose of amanitins lethal in a 70-kg adult.[4] The amanitins are not destroyed by cooking. α-Amanitin inhibits the RNA polymerase II, with 1:1 stoichiometry.[11] Inhibition of RNA polymerase II, which catalyses RNA synthesis, prevents DNA transcription and subsequent protein synthesis. Cell death follows.

Despite precise knowledge of the mechanism of action of the amanitins, we have no current therapy that is directed specifically against these actions of the toxins. No firm data support the use of thioctic acid, penicillin or corticosteroids.[3,4,9,12-15] For example, series of patients in whom thioctic acid was *not* used have mortality rates ranging from 0% to 26%, similar to the 0% to 24% rates when the drug was used.[3,4,9,12-15] In none of the studies were concurrent, placebo-treated controls used, and usually thioctic acid has been given with a number of other drugs such as dexamethasone, penicillin and neomycin. Nevertheless, the *Poisindex* still recommends the use of thioctic acid "until its value has been disproven, or a better treatment is found."[16]

All of our patients were given repeated doses of activated charcoal, either by mouth or through a duodenal tube. The goals were to absorb any unabsorbed amatoxin remaining in the gastrointestinal tract and to interrupt the enterohepatic circulation of the toxin,[7,17-19] as it does for other compounds.[20] Although this therapy has not been subjected to controlled studies, experimental data in dogs suggest that the rationale for this treatment is sound. Fauser and Faulstich administered radiolabelled methyl-γ-amanitins to three dogs that had external drainage of the bile and three control dogs.[19] The three control dogs died but the dogs with bile drainage did not.

Two of our patients underwent repeated charcoal hemoperfusion (cases 1 and 2); both these men died of their fulminant hepatic failure. The rationale for using hemoperfusion was that it might prevent the cerebral edema associated with fulminant liver failure,[21,22] not that it might remove the amanitins from the body.[23] Because concentrations of amanitins in serum of poisoned patients are low,[7] hemoperfusion probably removes insubstantial quantities from the body. It may remove greater amounts during absorption of the toxins or from patients with renal failure who are unable to excrete the toxins in the urine.[25,26] Because the kidney rapidly eliminates most of the absorbed dose of amatoxins, forced diuresis has some

theoretic value if a patient presents during the first few hours after admission.[17]

A porcine liver perfusion was done in each of two patients as an attempt to gain some time while their own livers regenerated. This cannot be recommended as a therapy, however, particularly due to poor results in these and in other patients[27] with fulminant hepatic failure.

Orthotopic liver transplantation was undertaken in a 3-year-old girl.[8] Experience with transplantation in acute liver failure is limited. In the National Institutes of Health Consensus Development Conference Summary on liver transplantation,[28] it was concluded that "although fulminant hepatic failure with massive hepatocellular necrosis induced by a number of agents may warrant liver transplantation, rapid progression of the disease and multiorgan system failure frequently preclude this option." The multiorgan failure and the number of hypotensive insults to the brain sustained during her hospital course probably contributed to our patient's permanent central nervous system deficits. Thus, the role of liver transplantation in amatoxin-poisoned patients, once they are obviously in fulminant liver failure, remains to be established.

The histopathologic findings in the liver biopsy specimens obtained from five patients during the acute illness showed massive centrilobular hepatic necrosis, similar to findings reported in another series.[29] The biopsy done eight weeks after ingestion in a 5-year-old boy (case 5) had evidence suggestive of cirrhosis, although the specimen was small and fragmented. This has not been reported before in other patients. Nor has the Fanconi-type renal tubular acidosis been observed, although one case of a patient whose primary manifestation of the intoxication was acute tubular necrosis has been reported.[26]

We used the radioimmunoassay for amanitins developed by Faulstich and co-workers to determine concentrations in a number of biologic specimens.[7] The limit of detection of the assay is about 3 ng of amanitins per ml. Applying the assay to serum specimens or to other biologic specimens such as bile or gastric juice was difficult both because of low concentrations of the amatoxins in these specimens and erratic quenching of counts. We currently recommend using the radioimmunoassay for urine or stool specimens collected within the first 24 hours to confirm the diagnosis if this is necessary. More patients will have to be studied, however, to establish any relationships between concentrations of the toxins and prognosis.

Our current approach to the treatment of an amatoxin-poisoned patient is to provide full supportive care for the early fluid and electrolyte loss and for the later hepatic failure.[27] We do not use any of the commonly recommended antidotes such as thioctic acid, penicillin or corticosteroids. Serum, urine and gastric aspirate or stool specimens are collected as early as possible if the clinical diagnosis requires confirmation by the amanitin radioimmunoassay. The toxins are removed through the gastrointestinal tract by giving repeated doses of activated charcoal orally (about 20 grams every 4 hours for 72 hours). If a patient is vomiting, we insert a duodenal tube to give the charcoal through the distal port and aspirate gastroduodenal fluid continuously from the proximal port. In this series of patients treated with intensive supportive care, 2 of the 22 patients died. The overall mortality of 9% provides a background on which the success of specific treatments should be judged.

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The Effects of Diuretics and Adrenergic-Blocking Agents on Plasma Lipids

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Antihypertensive medications cause the following changes in plasma lipids and lipoproteins: Thiazide and loop diuretics increase triglyceride, total cholesterol and low-density-lipoprotein (LDL) cholesterol levels with no change in high-density-lipoprotein (HDL) cholesterol. β-Adrenergic antagonists increase triglyceride and decrease HDL cholesterol levels. A rise in very-low-density-lipoprotein (VLDL) cholesterol balances the decrease in HDL cholesterol, so that there is no significant change in total cholesterol. α-Adrenergic antagonists decrease triglyceride, increase HDL cholesterol and may decrease VLDL and LDL cholesterol. Labetalol, with both α- and β-adrenergic antagonistic activity, does not affect plasma lipids in a small number of studies. The calcium channel blockers nifedipine and verapamil also have no consistent effect on lipoprotein levels in a small number of studies.

(Rohlfing JJ, Brunzell JD: The effects of diuretics and adrenergic-blocking agents on plasma lipids. West J Med 1986 Aug; 145:210-218)

The metabolic consequences of antihypertensive treatment using diuretics and adrenergic blocking agents are of increasing concern as hypertension is being diagnosed in more young and middle-aged persons and they are placed on lifelong therapy. While this practice is associated with a significant decrease in morbidity and mortality from renal failure, cardiac failure and cerebrovascular accidents,[1] several large prospective studies have failed to show a similar reduction in coronary heart disease in such persons.[2-4] The reason may be multifactorial; there is evidence of increased mortality in diuretic-treated persons with baseline electrocardiographic abnormalities, suggesting an etiologic role for electrolyte abnormalities.[5] In addition, it is becoming increasingly clear that many antihypertensive agents have an adverse effect on another coronary heart disease risk factor—plasma lipids.

Plasma lipids are composed of a number of subfractions, several of which have epidemiologic associations with coronary heart disease. The total cholesterol in a fasting person is the sum of very-low-density-lipoprotein (VLDL) cholesterol, low-density-lipoprotein (LDL) cholesterol and high-density-lipoprotein (HDL) cholesterol. The risk of coronary heart disease is directly proportional to the blood concentrations of LDL cholesterol and inversely proportional to the level of HDL cholesterol.[6] Although plasma triglyceride concentrations may not be directly related to a risk for coronary heart disease, they may serve as a marker for the presence of other risk factors such as other lipoprotein abnormalities, obesity or diabetes.

A substantial number of studies have expored the effects of antihypertensive agents on plasma lipid and lipoprotein levels. Many of these report rather large changes in certain plasma lipids, but because of a small number of subjects the findings have often not been statistically significant. Despite many differences in drug dosage, duration of treatment and laboratory methods, the observations for individual drugs have been surprisingly consistent. In this paper we review and summarize these studies (Figure 1).

The antihypertensive agents that have been best studied fall into four groups: thiazide and loop diuretics, β-adrenergic antagonists, α-adrenergic antagonists and calcium channel blockers. Two drugs do not fit well into these groups: labetalol hydrochloride, which is both a β- and an α-antagonist, and spironolactone, a potassium-sparing diuretic with properties distinct from the thiazide and loop diuretics. These agents are considered separately (Table 4). Because of inconsistent results from study to study, the actual percent changes in each variable were included in the tables even when not

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ABBREVIATIONS USED IN TEXT

HDL = high-density lipoprotein
ISA = intrinsic sympathomimetic activity
LDL = low-density lipoprotein
VLDL = very-low-density lipoprotein

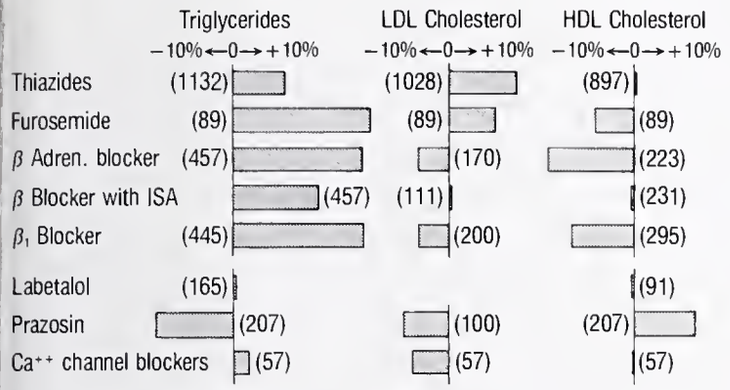

Figure 1.—Summary of data from studies in this review. Each person in each drug group in each manuscript is included (n>2,500). Values accompanying bars represent the number of persons in the stated drug group for which the specified lipoprotein was measured. Because the percent change could not be calculated for data from Lasser et al,[5] data from this study were not included. HDL = high-density-lipoprotein, ISA = intrinsic sympathomimetic activity, LDL = low-density-lipoprotein

statistically significant. This allows readers to make their own conclusions regarding trends of changes in plasma lipid and lipoprotein levels due to individual drugs.

Diuretics

Diuretics include the benzodiathiazide diuretics, the "loop" diuretics and the potassium-sparing diuretics. Benzodiathiazide and related diuretics, more commonly referred to as the thiazide diuretics, are currently the most frequently prescribed antihypertensives.[25] Alterations in lipid metabolism with these agents were first reported by Ames and Hill in 1976, when they found a 25% increase in plasma triglyceride levels in patients taking thiazides and a smaller but significant increase in cholesterol with the use of chlorthalidone.[7] Since this initial report, several authors have confirmed these findings (Table 1). The statistically significant changes include increases in triglyceride and cholesterol values. In addition, those studies reporting statistically insignificant changes reported, with few exceptions, rises in triglyceride and cholesterol levels.

Investigation into the alterations in plasma lipoprotein subfractions has shown that the increase in total cholesterol is associated with an increase in LDL-cholesterol levels. This finding was consistent and reached statistical significance in most studies. Changes in HDL cholesterol have been mixed,

TABLE 1.—*Effects of Thiazide and Loop Diuretic Therapy on Plasma Lipid and Lipoprotein Values**

Reference	*Drug*	*Dose, mg/d*	*Duration, wk*	*Patients, Number*	*Triglycerides*	*Total Cholesterol*	*VLDL-C*	*LDL-C*	*HDL-C*	*VLDL-C Plus LDL-C*	*LDL Determination Method†*	*Study Design‡*
Ames and Hill, 1976[7]	Chlor	Var	Var	32	↑25.7§	↑ 5.2§	...	...	...	...	...	A
Glück et al, 1978[8]	Chlor	100	4	16	↑10.0	↑ 4.0	↑30.0	↑ 8.0§	↓ 5.0	...	D	B
	Chlor	100	6	13	↑10.0	↑ 8.0	↑11.0	↑14.0§	↓12.0§	...	D	A
Glück et al, 1978[8]	Furo	80	4	16	↑16.0	↑ 6.0§	↑ 6.0	↑15.0§	↓ 4.0	...	D	B
	Mefru	50	4	16	↑14.0	↑ 5.0	↑20.0	↑10.0§	↑ 2.0	...	D	B
Ames and Hill, 1978[9]	HCTZ	Var	24	36	↑ 5.6	↑ 6.0§	...	...	...	...	...	A
Helgeland et al, 1978[10]	HCTZ	Var	208	26	↓13.0	↓ 2.4	...	...	↑ 1.4	...	...	A
Rosenthal et al, 1979[11]	Chlor	100	12	21	↑16.0§	↑ 7.8§	↑ 9.0	↑ 9.3§	↓12.0	...	D	A
Van Brummelen et al, 1979[12]	HCTZ	100	36	10	↑ 0.6	↑ 6.5§	...	...	↑ 7.5	...	...	A
Goldman et al, 1980[13]	Chlor	Var	52	508	↑ 7.6§	↑ 5.1§	...	↑10.2§	↑ 0.2	...	I	C
Glück et al, 1980[14]	Chlor	100	6	27	↑ 1.8	↑ 4.3	...	↑20.0§	↓ 3.4	...	D	A
	Chlor	100	6	10	↑ 7.7	↑ 0.9	...	↑ 4.0	↑10.0	...	D	A
Mordasini et al, 1980[15]	Chlor	100	6	12	↑11.0	↑10.6	↓ 5.0	↑15.0§	↓ 5.8	...	D	A
Crisp et al, 1980[16]	Cyclo	0.5	8	13	↑14.0	↑ 3.5	...	↑12.0	↓ 6.7	...	I	B
Leren et al, 1981[17]	HCTZ	50	10	10	↑ 6.1	↑ 2.6	...	...	↑ 2.4	↑2.6	...	B
Grimm et al, 1981[18]	HCTZ	100	6	41	↑17.0§	↑ 6.5§	↑12.5	↑ 5.6	↑ 6.3	...	D	B
	Chlor	100	6	41	↑15.0§	↑ 8.3§	↑ 6.8	↑ 9.5§	↑ 5.5	...	D	B
Weidmann et al, 1981[19]	Indap	2.5	6	18	↓ 8.8	↓ 0.5	...	↓ 1.0	0	...	D	A
Boehringer et al, 1982[20]	Chlor	100	6	22	↑ 4.4	↑ 1.4	↑35.0	↑ 3.0	↑ 2.1	...	D	A
	Chlor	100	6	18	↓ 6.8	↑13.0§	↓20.0	↑21.0§	↑20.0	...	D	A
VA Study, 1982[21]	HCTZ	Var	52	167	↓ 1.8	↓ 1.3	...	...	...	...	...	A
Johnson et al, 1984[22]	Poly	1	4	20	↑14.0§	↑ 4.2§	↑ 8.3	↑ 2.7	↑ 7.5	...	D	A
Lasser et al, 1984[5]	Chlor or HCTZ	100	312	1,021	↑35.0 mg/dl	↑ 4.0 mg/dl	...	↓ 0.7 mg/dl	↓ 0.8 mg/dl	...	I	C
	Chlor or HCTZ	100	312	785	↑37.0 mg/dl	↑ 6.6 mg/dl	...	↑ 1.7 mg/dl	↓ 1.4 mg/dl	...	I	C
Meyer-Sabellek et al, 1984[23]	Indap	2.5	24	12	↑19.0	↑ 5.8	↑31.0	↑ 0.6	↑ 7.5	...	D	A
Bloomgarden et al, 1984[24]	HCTZ	Var	...	89	↑10.0	↑11.0§	...	↑18.0§	0	...	I	E
	Furo	Var	...	57	↑20.0	↑ 2.0	...	↑ 3.0	↓ 6.5	...	I	E

Chlor = chlorthalidone, Cyclo = cyclopenthiazide, Furo = furosemide, HCTZ = hydrochlorothiazide, HOL-C = high-density-lipoprotein cholesterol, Indap = indapamide, LOL-C = low-density-lipoprotein cholesterol, Mefru = mefruside, Poly = polythiazide, Var = variable, VA Study = Veterans Administration Cooperative Study Group, VLOL-C = very-low-density-lipoprotein cholesterol, ↑ = increase, ↓ = decrease

*All lipid values are in percent change unless other units are given.
†O = direct measurement, I = indirect estimation.
‡A = single drug, uncontrolled, B = crossover; C = with a control group; E = cross-sectional.
§$P < .05$.

indicating that HDL-cholesterol levels are probably unaffected by the thiazide diuretics. As would be expected, changes in total plasma triglyceride are reflected in VLDL-cholesterol levels.

Because the duration of treatment in most studies was less than 12 weeks, the long-term effects of the thiazide diuretics on plasma lipids and lipoproteins are less clear. Helgeland and co-workers in 1978 reported an absence of significant change in plasma lipids after four years of hydrochlorothiazide therapy in 26 subjects as part of the Oslo study.[10] A trial by the European Working Party on High Blood Pressure in the Elderly again found no changes in plasma lipids after three years in patients treated with hydrochlorothiazide plus triamterene compared with a control group.[26] The Veterans Administration Cooperative Study Group reported a lack of change in plasma triglyceride or cholesterol levels after one year in 167 persons treated with hydrochlorothiazide. In contrast, other long-term studies document persistent significant increases in plasma triglyceride, cholesterol and LDL cholesterol values. The Veterans Administration-National Heart, Lung and Blood Institute cooperative trial reported a 7.6% increase in triglycerides, a 5.1% increase in cholesterol and a 10.2% increase in LDL-cholesterol levels in 508 patients treated with chlorthalidone for one year, all statistically significant changes.[13] Data from the Multiple Risk Factor Intervention Trial showed a persistent increase in triglyceride and cholesterol levels in both a series of men undergoing usual care and a group of men having special interventions after six years of thiazide treatment; also, there was a small, persistent increase in the LDL-cholesterol value in the men under usual care.[5]

The fact that the results of these long-term clinical trials have been inconclusive may relate to several variables. Simultaneous modifications of diet, exercise and body fat over the course of a study could diminish alterations in plasma lipids caused by the administered drug, making persistent changes in lipid concentrations difficult to show. Several observations support this hypothesis. Two groups of investigators have shown that a lipid-lowering diet can negate the elevation in cholesterol and LDL-cholesterol levels associated with the thiazide diuretics.[5,18] Trends in the American diet towards less saturated fat and cholesterol could have a similar effect. In addition, there is evidence that serum lipid levels tend to fall in normal, older persons as a part of the aging process.[26]

Interestingly, there is some evidence that drug-induced elevations in plasma lipids in women may be limited to the postmenopausal period. Boehringer and associates studied plasma lipid levels in thiazide-treated women and found a statistically significant increase in cholesterol and LDL-cholesterol concentrations only in the postmenopausal group.[20]

Glück and colleagues reported that the loop diuretics furosemide and mefruside cause the same alterations in plasma lipids as the thiazides. A significant increase in plasma LDL-cholesterol concentrations was found with both agents, in the absence of changes in triglyceride and HDL-cholesterol levels.[8]

Effects of the diuretic indapamide on plasma lipids were evaluated in two studies. Neither found significant effects on plasma lipid and lipoprotein values after six weeks of treatment with 2.5 mg per day.[19,23]

A few studies investigating the plasma lipid effects of spironolactone have yielded conflicting results (Table 4). In two, large increases in triglyceride levels were noted with no change in cholesterol values.[9,73] In a third recent study, significant increases in cholesterol and LDL-cholesterol levels occurred with only a small, insignificant increase in triglycerides.[27]

β-Adrenergic Antagonists

The term β-blocker encompasses many drugs that can be subdivided into nonselective agents antagonistic at both the β_1- and β_2-receptor and cardioselective agents specifically antagonistic for the β_1-receptor. A further subdivision of the nonselective group has been made because of the suggestion by Leren that those agents with intrinsic sympathomimetic activity (ISA) may behave differently from those without.[17] Several studies of nonselective and cardioselective β-blockers have shown a significant increase in plasma triglyceride levels (Table 2). In fact, several investigators have found triglyceride increases in excess of 50% of baseline.[33,36,45] Long-term studies indicate that this elevation in triglyceride levels persists beyond the early treatment period. The Veterans Administration Cooperative Study Group found a 25% increase in triglyceride values in 118 patients treated with propranolol hydrochloride for one year.[21] Lehtonen and Viikari reported a 66% increase in triglyceride values after one year of sotalol hydrochloride treatment in 12 patients.[36] Several studies show these changes to last six to eight months during treatment with the cardioselective agents as well.[34,57,60]

While plasma total cholesterol does not appear to be affected by β-adrenergic blockade, changes in the concentrations of individual plasma lipoprotein cholesterols do occur. The most important of these in relation to cardiovascular risk is an impressive reduction in plasma HDL-cholesterol levels found with both nonselective and cardioselective agents. All of the observed statistically significant changes in HDL-cholesterol concentrations have been reductions, and the trend has been a reduction for most of the insignificant changes as well. Lehtonen and co-workers found this reduction in HDL-cholesterol values to persist for at least six months with atenolol[60] and one year with sotalol treatment.[36] Several investigators have found that the decrease in plasma HDL-cholesterol levels with β-adrenergic blockade is balanced by an increase in VLDL-cholesterol levels[34,57,59] and that the combined changes result in a lack of net change in total cholesterol.

Plasma LDL-cholesterol levels have decreased with β-blockade in many studies that have quantified this value, but the change has been statistically significant in only two.[40,44] It is important to note that both studies calculated LDL cholesterol indirectly. Calculated changes in LDL-cholesterol levels may be misleading, as this method assumed VLDL cholesterol to be equivalent to the triglyceride value divided by 5, a relationship that may change with altered lipoprotein metabolism. At this point one might conclude that changes in the LDL-cholesterol value are insignificant.

Dujovne and associates compared the effects of propranolol treatment in patients with normal lipid levels with effects in persons with type II-A and type II-B hyperlipoproteinemia. They found an increase in triglyceride levels in the persons with normal lipid levels, whereas the persons with hyperlipidemia also showed small but statistically significant in-

TABLE 2.—*Effects of β-Adrenergic Antagonists on Plasma Lipid and Lipoprotein Values**

Reference	Drug	Dose, mg/d	Duration, wk	Patients, Number	Triglycerides	Total Cholesterol	VLDL-C	LDL-C	HDL-C	VLDL-C Plus LDL-C	LDL Determination Method†	Study Design‡
Nonselective β-Blocker Without ISA												
Lloyd-Mostyn et al, 1971[28]	Propran	40	2	12	↑30.0	↓ 3.6	...	...	...	...	...	B
Tanaka et al, 1976[29]	Propran	60	8	10	↑ 9.7	↓ 8.6	...	...	...	...	D	A
Brunzell et al, 1977[30]	Propran	Var	...	14	↑72.0§	↑16.0	...	...	...	...	...	C
Shaw et al, 1978[31]	Propran	Var	4	17	↑37.0§	↑ 3.6	...	...	...	...	...	B
Streja and Mymin, 1978[32]	Propran	Var	2	16	↓ 0.4	↓ 5.8	...	↓ 2.6	↓12.0§	...	...	A
Day et al, 1979[33]	Propran	Var	24	16	↑65.0§	↑ 6.0	...	...	...	...	...	A
Bielmann and Leduc, 1979[34]	Propran	160	8	6	↑98.0	...	↑64.0§	↓17.9	↓22.0§	...	D	B
Wright et al, 1979[35]	Propran	160	4	20	↑ 17.0	↓ 1.5	...	...	...	...	...	B
Lehtonen and Viikari, 1979[36]	Sotalol	Var	52	12	↑66.0§	↑16.0§	...	...	↓26.0§	↑32.0§	I	A
Leren et al, 1981[37]	Propran	160	8	23	↑ 23.0§	↓ 1.0	...	...	↓13.0§	↑ 2.1	...	B
Ponti et al, 1983[38]	Propran	160	6	11	↑ 25.0§	↑ 9.1§	...	...	↓ 7.6	...	...	B
Day et al, 1982[39]	Propran	160	12	53	↓51.0§	↓ 1.4	...	↓ 6.1	↓17.0§	...	D	B
Birnbaum et al, 1982[40]	Propran	Var	8	20	↑25.0§	↓ 5.6§	...	↓ 9.0§	↓ 7.0	...	I	B
VA Study, 1982[21]	Propran	Var	52	118	↑25.0§	↑ 3.9§	...	...	...	...	...	A
Goto, 1984[41]	Propran	Var	12	26	↑17.0	↑ 1.0	...	...	↓ 2.0	↑ 2.0	...	A
Lowenstein and Neusy, 1984[42]	Propran	Var	8	29	↑ 0.8	↓ 0.8	...	↑ 0.5	↓ 1.3	...	I	B+D
Johnson et al, 1984[22]	Propran	Var	12	20	↑22.7§	↑ 1.3	↑30.0§	0	↓ 9.6§	...	D	B+D
Dujovone et al, 1984[43]	Propran	Var	12	8	↑37.0§	↑ 1.0	↑44.0	↓ 5.4	↓ 4.3	...	D	B
	Propran	Var	12	9	↑ 5.0	↑ 1.3§	↓ 3.0	↑ 2.3§	↓ 2.2	...	D	B
Murphy et al, 1984[44]	Propran	320	12	9	↑ 7.5	↓ 6.3§	↓ 8.5§	↓ 8.5§	↓ 2.1	...	I	A
With ISA												
England et al, 1978[45]	Pindolol	Var	4	17	↑28.0§	↑ 5.4	...	...	...	...	...	B+D
Leren et al, 1981[17]	Pindolol	Var	10	10	↓ 9.0	↓ 4.6	...	...	↑ 3.9	↓ 6.6	...	A
Pasotti et al, 1982[46]	Pindolol	Var	12	16	↑ 1.8	↑ 0.3	...	↓ 3.6	↑20.0§	...	I	B
Lehtonen et al, 1982[47]	Pindolol	Var	24	20	↑ 0.9	↓ 4.3§	...	...	↑ 3.5	...	...	A
Karmakoski et al, 1983[48]	Pindolol	Var	16	13	↓17.0	↑ 1.5	...	↑18.0	↑12.0	...	D	C
Murphy et al, 1984[44]	Pindolol	20	12	8	↓ 6.8	↓ 8.9	...	↓10.8	↓ 4.6	...	I	A
Lloyd-Mostyn et al, 1971[28]	Oxpren	40	2	10	↑ 3.3	↑ 0.3	...	...	...	...	...	B
Sommers et al, 1981[49]	Oxpren	120	3	80	↑ 6.8	↓12.7§	...	...	0	...	...	B
Ballantyne et al, 1981[50]	Oxpren	160	16	9	↑13.0	↑ 7.0	↓ 3.0	↑11.0	↑ 1.4	...	D	A
Kjeldsen et al, 1982[51]	Oxpren	160	18	10	↑20.0	↑ 1.2	...	...	↓11.4§	↑ 4.1	...	A
Day et al, 1982[39]	Oxpren	160	12	53	↑26.0§	↓ 0.3	...	↓ 3.9	↓11.5§	...	D	B
Simons et al, 1982[52]	Oxpren	Var	32	12	↑33.0§	↑ 7.0	↑50.0	↑ 7.3	↑11.5	...	D	A
β_1-Blockers												
Lloyd-Mostyn et al, 1971[28]	Pract	200	2	12	↑ 7.5	↓ 2.0	...	...	...	...	...	B
Waal-Manning, 1976[53]	Metop	...	12	14	↑34.0§	↓ 2.5	...	...	...	...	...	A
Nilsson et al, 1977[54]	Metop	Var	12	9	↓10.0	...	...	...	...	...	...	A
England et al, 1978[45]	Atenolol	100	4	17	↑62.0§	↑ 2.1	...	...	...	...	...	B+D
	Metop	100	4	17	↑32.0§	↑ 2.0	...	...	...	...	...	B+D
Day et al, 1979[33]	Atenolol	Var	24	14	↑24.0§	↑ 1.6	...	...	...	...	...	A
Bielmann and Leduc, 1979[34]	Metop	200	8	6	↑40.0	...	↓ 4.8	↓ 8.6	↑ 6.1	...	D	B
Wright et al, 1979[35]	Metop	200	4	20	↑13.2	↑ 0.9	...	...	...	...	...	B
Beinart et al, 1979[55]	Metop	200	12	12	0	↑ 8.6	...	...	...	...	...	A
England et al, 1980[56]	Metop	Var	12	34	↑10.0§	↓ 1.0	...	...	↓13.0§	...	...	B
	Atenolol	100	12	34	↑ 6.0§	↓ 0.8	...	...	↓10.0	...	...	B
Eliasson et al, 1981[57]	Atenolol	100	32	15	↑26.0§	↑ 7.4	↑29.0§	↑ 3.7	↓ 1.6	...	D	A
Thulin et al, 1981[58]	Atenolol	Var	6	33	↑27.0§	↓ 1.7	...	...	...	...	...	B
Kjeldsen et al, 1982[51]	Atenolol	100	18	9	↑17.9§	↓ 1.6	...	...	↓16.5	↑ 2.6	...	A
Day et al, 1982[39]	Atenolol	100	12	53	↑24.0§	↑ 3.1	...	↓ 5.2	↓ 7.0§	...	D	B
	Metop	200	12	53	↑14.0§	↓ 1.4	...	↓ 4.4	↓13.0§	...	D	B
Birnbaum et al, 1982[40]	Acebut	Var	8	17	↓ 2.1	↓ 7.4	...	↓12.0§	↓ 2.4	...	I	B
Pasotti et al, 1982[46]	Metop	Var	12	16	↑ 0.5	↑ 3.1	...	↑ 4.7	↑ 0.7	...	I	B
Rössner and Weiner, 1983[59]	Atenolol	50	12	20	↑ 6.4	↓ 2.8	↑ 4.0	↓ 1.5	↓ 2.1	...	D	B
	Metop	200	12	20	↓ 4.0	↑ 2.5	↑29.0§	↓ 3.2	↓ 7.7§	...	D	B
Lehtonen and Marniemi, 1984[60]	Atenolol	100	24	18	↑37.0§	8.0§	...	...	↓11.8§	...	...	A

Acebut = acebutolol, HDL-C = high-density-lipoprotein cholesterol, ISA = intrinsic sympathomimetic activity, LDL-C = low-density-lipoprotein cholesterol, Metop = metoprolol, Oxpren = oxprenolol hydrochloride, Pract = practolol, Propran = propranolol hydrochloride, Var = variable, VA Study = Veterans Administration Cooperative Study Group, VLDL-C = very-low-density-lipoprotein cholesterol, ↑ = increase, ↓ = decrease

*All lipid values are in percent change unless other units are given.
†D = direct measurement, I = indirect estimation.
‡A = single drug, uncontrolled, B = crossover; C = with a control group; D = studied drug added as a second drug, first drug listed in footnote.
§$P < .05$.

creases in total cholesterol and LDL-cholesterol levels with no change in triglycerides.[43]

Leren and colleagues reported in 1981 that pindolol, a nonselective β-blocker, did not appear to affect triglyceride or lipoprotein levels and speculated that this might be due to the high intrinsic sympathomimetic activity of the drug.[17] Unlike other β-blockers, pindolol may cause the HDL-cholesterol level to rise, with increases as high as 20% reported.[46] England and co-workers found a 28% increase in triglycerides when pindolol was added to a regimen with chlorothiazide,[45] but either no change or statistically nonsignificant decreases in triglyceride levels have been reported in other studies.

Oxprenolol hydrochloride is another nonselective β-blocker that possesses ISA. Two studies have found statistically significant decreases in plasma HDL-cholesterol values of about 11%.[39,51] Day and colleagues found triglyceride levels to be elevated significantly with the use of oxprenolol[39]; other studies showed a trend for triglyceride levels to increase. Thus, the effects on plasma lipid and lipoprotein values associated with oxprenolol treatment are more similar to those noted with β-blockers without ISA than to those occurring with the use of pindolol. This is probably related to the relative ISA potency of the two drugs, with pindolol having greater partial β-agonist activity than oxprenolol.[62]

α-Adrenergic Antagonist

Prazosin hydrochloride, an α_1-antagonist, has stirred considerable interest since Leren and associates reported in 1981 that this drug may have a beneficial effect on plasma lipids and lipoprotein levels. In a crossover trial of propranolol in seven subjects, Leren and co-workers found prazosin therapy to significantly reduce triglycerides, total cholesterol and the sum of VLDL cholesterol plus LDL cholesterol, with no change in HDL-cholesterol levels.[37] Since this report, a number of studies have been conducted investigating plasma lipid and lipoprotein changes with prazosin therapy (Table 3). In many studies designed with prazosin added to a previous drug regimen, the results have been quite consistent and include a reduction in triglyceride and an increase in HDL-cholesterol levels. There has been a trend of a decrease in cholesterol, but the change has not been large. A few studies investigating changes in VLDL- and LDL-cholesterol levels have found decreases in both of these lipoproteins, with two groups reporting statistically significant reductions. Rouffy and Jaillard reported that the mean LDL-cholesterol level decreased 13% and VLDL cholesterol 18%.[71] Lowenstein and Neusy reported a 9.4% reduction in LDL-cholesterol concentrations with prazosin therapy.[42] In conclusion, prazosin tends to lower triglyceride, raise HDL cholesterol and may also lower LDL- and VLDL-cholesterol concentrations.

Two studies have focused on the plasma lipid changes with prazosin therapy given for one year. Lithell and associates failed to observe significant changes in plasma lipids after one year,[68] whereas Takabatake and associates reported a persistent increase in HDL-cholesterol levels after the same period.[72]

α- and β-Adrenergic Antagonists

Labetalol is a nonselective β-blocker that also has α-antagonistic activity. This drug recently was released for use in the United States. Five studies have evaluated changes in triglyceride levels with labetalol hydrochloride therapy, with four reporting nonsignificant increases (Table 4).[39,49,58,74] Changes in plasma HDL-cholesterol values were assessed in only two studies, with one reporting no change and the other a nonsignificant decrease.[39,49] Sommers and colleagues reported no change in HDL-cholesterol levels but found a statistically significant decrease in total cholesterol of 14%.[49] No studies have investigated changes in LDL- or VLDL-cholesterol values with the use of labetalol.

Calcium Channel Blockers

Calcium channel blockers are relatively new agents that are rapidly becoming popular in the treatment of angina and hypertension. Nifedipine and verapamil, two members of this

TABLE 3.—*Effects of α-Antagonist (Prazosin Hydrochloride) Therapy on Plasma Lipid and Lipoprotein Values**

Reference	Dose, mg/d	Duration, wk	Patients, Number	Triglycerides	Total Cholesterol	VLDL-C	LDL-C	HDL-C	VLDL-C Plus LDL-C	LDL Determination Method†	Study Design‡
Kirkendall et al, 1978[63]	Var	8	13	...	↓ 5.3§	...	...	...	...	...	A
Leren et al, 1980[37]	4	8	7	↓16.5§	↓ 9.0§	...	...	↓ 4.0	↓10.0§	...	B
Leichter and Baumgardner, 1981[64]	Var	Var	7	↑ 4.0	↓ 4.3	...	...	↑ 6.0	...	...	A+D
Velasco et al, 1982[65]	Var	12	19	↓27.0	↑ 7.5	↓22.0	↓ 2.2	↑19.6	...	D	A+D
Kokubu et al, 1982[66]	Var	12	14	↑ 0.9	↓ 0.7	...	...	↑12.5	↓ 4.5	...	A
Havard et al, 1982[67]	Var	8	17	↓14.0	↓ 0.9	...	...	↑ 7.7	...	...	A
Lithell et al, 1982[68]	Var	52	8	↓ 0.7	↓ 3.2	↓15.0	↓ 6.5	0	...	D	A
Goto, 1984[41]	Var	12	17	↓21.0§	↓ 1.1	...	...	↓ 4.0	↓ 4.2	...	A+D
Lowenstein and Neusy, 1984[42]	Var	8	29	↓20.0§	↓ 7.3§	...	↓ 9.4§	↑ 6.0§	...	I	A+D
Kather and Sauberlich, 1984[69]	Var	12	15	↑ 6.8	↑ 2.8	...	...	↑ 8.5§	...	...	A
Mauersberger, 1984[70]	Var	8	15	↓ 3.2	↓ 2.3	...	...	↑10.9§	...	...	A+D
Rouffy and Jaillard, 1984[71]	Var	13	24	↓ 9.8§	↓ 7.9§	↓19.0§	↓13.0§	↑13.0§	...	D	A
Johnson et al, 1984[22]	Var	12	20	↓ 5.7	↑ 2.3	↓12.0	↑ 4.7	↑ 3.9	...	D	B+D
Takabatake et al, 1984[72]	Var	52	15	↓ 7.3	↑ 2.0	...	...	↑17.0§	...	...	A

HOL-C = high-density-lipoprotein cholesterol, LDL-C = low-density-lipoprotein cholesterol, Var = variable, VLDL-C = very-low-density-lipoprotein cholesterol, ↑ = increase, ↓ = decrease

*All lipid values are in percent change unless other units are given.
†D = direct measurement, I = indirect estimation.
‡A = single drug, uncontrolled; B = crossover; O = studied drug added as a second drug.
§$P < .05$.

class, have been investigated for their effects on plasma lipids (Table 4). Vessby and co-workers reported in 1983 that nifedipine failed to significantly alter plasma lipid and lipoprotein values in 11 subjects.[79] In a study of verapamil in 12 patients, 10 with angina, Walldius found statistically significant decreases in both total and LDL-cholesterol concentrations.[76] Two other investigators failed to verify this, although they did find insignificant decreases in LDL-cholesterol levels.[77,78]

Diabetes Mellitus and Antihypertensive Therapy

In several studies persons with diabetes mellitus had alterations in plasma lipids similar to those without diabetes when treated with various antihypertensive drugs. Bloomgarden and associates found a significantly higher level of LDL cholesterol in a cross-sectional study of patients with diabetes treated with thiazides compared with diabetic patients not receiving drugs.[24] Other studies of patients with diabetes found nonsignificant elevations in triglyceride levels when treated with propranolol or metoprolol[35] and a nonsignificant elevation in HDL-cholesterol concentrations when treated with prazosin.[64]

Pronounced hypertriglyceridemia (a triglyceride level of greater than 2,000 mg per dl as chylomicrons and VLDL) has been reported in persons with diabetes treated with β-adrenergic blocking agents or diuretics.[80] These patients are unique in that they have inherited both a familial form of hypertriglyceridemia and the propensity for diabetes mellitus. The simultaneous inheritance of these two independent disorders appears to make them particularly sensitive to these agents.[81]

HDL-Cholesterol Subfractions

There is evidence that the HDL-cholesterol subfraction HDL_2 may be a better predictor of coronary artery disease than HDL cholesterol.[83] In several recent studies the effects of antihypertensive drugs on HDL-cholesterol subfractions were investigated (Table 5). Lehtonen and Marniemi and Meltzer and associates found that the decreases in HDL-cholesterol levels seen with the use of β-blockers were primarily due to decreases in HDL_2, without a significant change in the HDL_3 subfraction.[60,82] Rouffy and Jaillard also found a decrease in HDL-cholesterol levels with atenolol therapy to be associated with a decrease in HDL_2.[71] In single studies, the use of the drugs prazosin and verapamil have been associated with increases in the HDL_3 subfraction.[76,82]

Apoproteins

In addition to the individual lipoproteins discussed previously, apoproteins have a predictive value for coronary artery disease. Specifically, persons with coronary artery disease have had elevated levels of apoprotein B compared with controls matched for total cholesterol and triglyceride levels.[84] The ratio of apoprotein A-I to apoprotein A-II, both of which are found in HDL cholesterol, can be used as a rough guide to changes in HDL_2 levels. An increase in this ratio is associated with an elevation in HDL_2.[85] Changes in specific apoprotein levels with antihypertensive medications have been evaluated by several investigators (Table 6).

The thiazide diuretics significantly altered apoprotein levels in only one study. Boehringer and colleagues found a 16% increase in apoprotein B levels in postmenopausal women treated with chlorthalidone.[20] Other studies show a trend towards an increase in apoprotein B that parallels the increase in LDL-cholesterol values. Changes in apoproteins A-I and A-II have been nonsignificant.

β-Blockade has been found to decrease apoprotein A-I in a study by Rouffy and Jaillard and to decrease apoprotein A-I plus A-II levels in a study by England and co-workers.[56,71] This result is in agreement with the previously mentioned decreases in HDL cholesterol. Although Rouffy and Jaillard have found a significant increase in apoprotein B values with

TABLE 4.—*Effects of Spironolactone, Labetalol and Calcium Channel Blocker Therapy on Plasma Lipid and Lipoprotein Values**

Reference	Dose, mg/d	Duration, wk	Patients, Number	Triglycerides	Total Cholesterol	VLDL-C	LDL-C	HDL-C	VLDL-C Plus LDL-C	LDL Determination Method†	Study Design‡
Spironolactone											
Ames and Hill, 1978[9]	Var	24	20	↑19.0§	↑ 2.2	...	...	...	...	...	A
Schersten et al, 1980[73]	200	8	45	↑13.0§	↑ 1.6	...	...	...	...	...	A
Hunninghake et al, 1984[27]	100	6	...	↑ 5.8	↑ 3.6§	...	↑ 5.3§	↓ 1.5	...	...	B
Labetalol											
Pagnun et al, 1979[74]	Var	16	8	↑27.0	↓ 1.6	...	...	...	...	...	A
McGonigle et al, 1981[75]	...	52	33	↓12.0	↓ 4.0	...	...	...	...	...	A
Sommers et al, 1981[49]	300	3	80	↑ 2.0	↓14.0§	...	...	0	...	...	B
Thulin et al, 1981[58]	Var	6	33	↑ 6.7	↑ 3.3	...	...	...	...	...	B
Day et al, 1982[39]	400	6	11	↑ 1.2	↑ 6.6	...	...	↓ 7.4	...	...	B
Calcium Channel Blockers—Verapamil											
Walldius, 1982[76]	Var	24	12	↓ 8.1	↓ 7.6§	↓15.0	↓ 8.5§	↓ 0.7	...	D	A
Faergeman et al, 1982[77]	360	24	13	↑ 9.0	↓ 5.5	↑66.0	↓12.0	↓ 8.0	...	D	C
Strunge et al, 1982[78]	...	24	21	↓ 1.3	↑ 6.7	...	↓ 1.7	↓ 1.0	...	I	C
Nifedipine											
Vessby et al, 1983[79]	80	12	11	↑13.0	...	↓11.0	↓ 0.2	↑ 9.5	...	D	A

HDL-C = high-density-lipoprotein cholesterol, LDL-C = low-density-lipoprotein cholesterol, Var = variable, VLDL-C = very-low-density-lipoprotein cholesterol, ↑ = increase, ↓ = decrease

*All lipid values are in percent change unless other units are given
†D = direct measurement, I = indirect estimation.
‡A = single drug, uncontrolled; B = crossover; C = with a control group.
§$P < .05$.

TABLE 5.—*Drug Therapy and High-Density-Lipoprotein Cholesterol (HDL-C) Subfractions**

Reference	Drug	HDL-C	HDL_2	HDL_3
Murphy et al, 1984[44]	Propranolol hydrochloride	↓ 2.1	↓16.0	↑ 5.9
	Pindolol	↓ 4.6	↓ 6.1	↓ 3.8
Lehtonen and Marniemi, 1984[60]	Atenolol	↓12.0†	↓28.0†	↓ 3.8
Rouffy and Jaillard, 1984[71]	Atenolol	↓10.0†	↓ 6.1†	...
Waldius, 1982[76]	Verapamil	↓ 0.7	↓ 8.7	↑12.0†
Meltzer et al, 1984[82]	Propranolol	↓21.0†	↓23.0†	↓15.0
	Prazosin hydrochloride	↑ 9.9	↓ 6.7	↑26.0†

↑ = increase, ↓ = decrease

*Values represent percent change.
†$P \leq .05$.

TABLE 6.—*Effects of Adrenergic-Blocking Agents on Apoproteins**

Reference	Drug	Apoproteins B	Apoproteins A-I	Apoproteins A-II
Glück et al, 1980[14]	Chlorthalidone	↑ 2.8	0	↓2.6
	Chlorthalidone	↑ 5.3	↓ 0.8	↑1.9
Mordasini et al, 1980[15]	Chlorthalidone	↑ 9.8	↓ 1.7	↓7.5
Weidmann et al, 1981[19]	Indapamide	↓ 2.7	...	...
Boehringer et al, 1982[20]	Chlorthalidone	0	↓ 4.8	↓2.3
	Chlorthalidone	↑16.0†	↓ 4.7	↓7.8
England et al, 1980[56]	Metoprolol	↓ 2.3	↓ 9.1† (A-I plus A-II)	
	Atenolol	↓13.0	↓ 9.8† (A-I plus A-II)	
Lithell et al, 1982[68]	Prazosin hydrochloride	↓ 2.5	↑ 1.9	↓3.1
Rouffy and Jaillard, 1984[71]	Atenolol	↑ 2.9†	↓ 6.4†	...
	Prazosin	↓ 7.3†	↑11.0†	...

↑ = increase, ↓ = decrease

*Values represent percent change.
†$P \leq .05$.

atenolol therapy,[71] significant changes in this apoprotein have not been found by other authors. α-Blockade with the use of prazosin was found by Rouffy and Jaillard to cause a decrease in apoprotein B and an increase in apoprotein A-I levels.[71] Lithell and associates found no significant changes in the apoproteins with prazosin, however.[68]

Discussion

From the above observations, it is possible to make some general mechanistic speculations as to how the described drugs cause their characteristic changes in lipid and lipoprotein concentrations. β-Blockade appears to increase plasma triglyceride and decrease HDL-cholesterol levels, whereas α-blockade seems to cause a decrease in triglyceride and an increase in HDL-cholesterol levels. These findings support a theory first described by Day and colleagues that unopposed α-stimulation may be responsible for the decrease in HDL cholesterol and an increase in triglyceride levels seen with β-blocker treatment.[39] Day and co-workers proposed that unopposed α-stimulation causes these changes through the inhibition of lipoprotein lipase.[39] There is no direct evidence that this occurs, however. Attempts to infer that a decreased Intralipid (an emulsion of soybean triglyceride and phospholipid) clearance[39] associated with β-blocker therapy represents adrenergic inhibition of lipoprotein lipase[86] may be misleading. The lipoprotein lipase triglyceride removal system is a saturable enzyme system in humans.[87] The delayed clearance of Intralipid may reflect an increase in serum triglyceride levels due to an increased input of very-low-density lipoprotein; a relative defect in clearance may be due to the increase in input.

Hooper and associates in 1981 reported a 10% increase in plasma HDL cholesterol with the use of terbutaline, an adrenergic agonist relatively selective for the β_2-receptor.[88] This evidence, plus reports of antagonistic effects of α- and β-activity on human adipocyte activity,[69,89] led to the proposal that changes in triglyceride and HDL-cholesterol levels are related to the ratio of total α- and β-activity, with an increase in the ratio (as with β-blockade) leading to increased triglyceride and decreased HDL-cholesterol levels; a decrease in the ratio (as with α-blockade) leads to decreased triglyceride and increased HDL-cholesterol values. Labetalol, with both α- and β-adrenergic antagonistic activity, would not be expected to greatly alter this adrenergic ratio. Similarly, pindolol, a partial agonist of the β-receptor, acts as both a β-adrenergic agonist and antagonist and would not greatly alter this adrenergic ratio.

It is possible to relate the thiazide- and loop diuretic-induced elevations in triglyceride levels to the above scheme. These agents, through a depletion of intravascular volume, cause a reactive elevation in plasma catecholamine levels with an increase in α-adrenergic activity. There does not appear to be a concomitant decrease in HDL-cholesterol concentrations, however, as would be predicted by the above hypothesis. Further, the mechanism for the increase in LDL cholesterol seen with these agents is obscure.

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Antihypertensive Therapy, Serum Lipids, Coronary Heart Disease and Hypertension—Balancing the Risks and Benefits of Treatment

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In 1931 a British physician named Hay stated that "the greatest danger to a man with high blood pressure lies in its discovery because then some fool is certain to try and reduce it" (*British Medical Journal* 1931; 2:43-47). Although this seems a somewhat radical statement, recent large clinical trials and laboratory observations lend credence to this proposal as it relates to the lack of reduction in morbidity and mortality in coronary heart disease by treating chronic hypertension.

Reducing blood pressure decreases the complications of hypertensive arteriolar disease (congestive heart failure, renal insufficiency and cerebrovascular accidents) in all degrees of hypertension.[1-11] Atherosclerotic complications, however—such as coronary heart disease, myocardial infarction, angina and peripheral vascular disease—have not been reduced in the majority of clinical studies designed to determine if pharmacologic control of chronic mild to moderate hypertension decreases coronary heart disease and its complications.[1-11]

It has been proposed that pharmacologic treatment of mild or moderate hypertension (diastolic blood pressure of 110 mm of mercury or less) with the traditional stepped-care regimen using diuretics and β-blockers may outweigh or partially or completely cancel the treatment benefits, particularly as they relate to the incidence of coronary heart disease, ventricular arrhythmias and sudden death due to medication-induced adverse metabolic changes that unfavorably alter known risk factors for coronary heart disease.[12-16] Specifically, adverse changes in serum lipids, lipid subfractions (high-density-lipoprotein cholesterol), low-density-lipoprotein cholesterol, lipoproteins, glucose, exercise tolerance, left ventricular hypertrophy and other risk factors for coronary heart disease could account for the lack of reduction in coronary heart disease in most studies[1,2,6,7,9,11] or an actual increase in the coronary heart disease death rate in treated patients in other clinical studies.[3,5,8,10]

There are more than 60 million people in the United States with a blood pressure exceeding 140/90 mm of mercury.[17] Approximately 80% to 90% of these patients have a diastolic blood pressure of less than 110 mm of mercury.[17] Coronary heart disease is the major complication among these patients and is the leading cause of death in the United States.[18-20] More than 600,000 deaths each year are attributed to coronary heart disease at an annual cost of $60 billion.[18-20] Unfortunately, antihypertensive pharmacologic therapy to date has *not* conclusively reduced the incidence of coronary heart disease in patients with mild to moderate hypertension.[1-11]

There are 11 major clinical trials published to date that have attempted to answer the question, does reducing the blood pressure reduce coronary heart disease? Careful analysis of these studies indicates that the coronary heart disease risk was reduced in one study in treated patients,[4] unchanged in six studies in treated patients[1,2,6,7,9,11] and *increased* in four studies in treated patients.[3,5,8,10] In all of these studies except the Hypertension Detection Followup Program (HDFP)[4] and the European Working Party on Hypertension in the Elderly,[9] the patients in the treated group received initial therapy with a thiazide diuretic or chlorthalidone in high doses (50 to 100 mg per day) and, if the blood pressure was not satisfactorily controlled, the second drug added to the thiazide regimen was a β-blocker (usually propranolol hydrochloride). Additional third-step drugs included methyldopa, reserpine or hydralazine hydrochloride. The HDFP,[4] the only study to show a reduction in coronary heart disease risk in treated patients, used a different antihypertensive regimen. The majority of patients were given a diuretic as initial therapy followed by reserpine or methyldopa. Only 300 patients received a β-blocker. Also of note is that the reduction in risk for coronary heart disease was limited to patients older than 50 years who had a diastolic blood pressure of 90 to 94 mm of mercury, had not previously received antihypertensive therapy and had no end-organ damage. Of even more concern is that in white men, white women and black women there was a greater morbidity and mortality from coronary heart disease in the treated patients who had preexisting electrocardiographic (ECG) abnormalities compared with the untreated patients.[4]

(Houston MC: Antihypertensive therapy, serum lipids, coronary heart disease and hypertension—Balancing the risks and benefits of treatment. West J Med 1986 Aug; 145:219-221)

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Reprints are not available.

ABBREVIATIONS USED IN TEXT

ECG = electrocardiogram
HDFP = Hypertension Detection Followup Program
ISA = intrinsic sympathomimetic activity
MRFIT = Multiple Risk Factor Intervention Trial

It is speculated that the limited use of β-blockers in the HDFP study resulted in less adverse effects on coronary heart disease risk factors and thus the coronary heart disease risk compared with that of all other studies where diuretics and β-blockers were both used.

In the Multiple Risk Factor Intervention Trial (MRFIT),[8] the stepped-intervention, aggressively treated patients had a higher coronary death rate (14.7 per 1,000) compared with the usual-care, less aggressively treated patients (10.2 per 1,000) in the group with a diastolic blood pressure of 90 to 94 mm of mercury. Patients with abnormal ECGs treated with a diuretic had a higher coronary death rate than those with abnormal ECGs who were not treated.

The Medical Research Council Trial[7] of 17,354 men and women between ages 35 and 64 with a diastolic blood pressure of 90 to 109 mm of mercury used placebo, a thiazide diuretic or propranolol for five years. Although the active-treatment group had a significantly reduced stroke rate, the coronary heart disease rate in the treatment groups did not significantly differ from the rates in the placebo group. In addition, β-blocker therapy was less effective in reducing the stroke rate than was diuretic therapy.

Although these unexpected results are unexplained and there exist vociferous arguments to support various viewpoints, it is plausible that the diuretics and β-blockers used in these trials induced long-term abnormal lipid profiles that accelerated coronary heart disease and that high-dose diuretic therapy predisposes patients with an abnormal ECG (coronary heart disease, left ventricular hypertrophy, arrhythmias and the like) to sudden death from a fatal arrhythmia due to hypokalemia or hypomagnesemia, particularly at times of stress or during or after exercise.[12-16]

In this issue of the journal, Rohlfing and Brunzell have reviewed the effects of numerous antihypertensive drug regimens on plasma lipids that may explain many of the previous observations. Antihypertensive drugs can be divided into three major groups based on their effects on serum lipids. Those agents with a favorable effect on serum lipids include clonidine,[21,22] guanabenz[23] and prazosin.[24,25] Those with unfavorable effects on serum lipids are thiazide and thiazidelike diuretics,[26-28] chlorthalidone[12,13] and loop diuretics,[12,13] but not spironolactone.[12,13,28] The data on metolazone and indapamide are conflicting.[29] In addition, all β-blockers without intrinsic sympathomimetic activity (ISA)[30] (propranolol, nadolol, metoprolol, atenolol and timolol), methyldopa[31-33] and reserpine[12,13] have an unfavorable effect on serum lipids. The antihypertensive drugs that have a neutral effect on lipids include the β-blockers with ISA[30] (pindolol and acebutolol), hydralazine hydrochloride,[34] minoxidil, angiotensin-converting enzyme inhibitors (captopril and enalapril maleate)[35] and calcium channel blockers (nifedipine, diltiazem, verapamil).[36,37] However, recent studies have suggested that calcium blockers may have favorable effects on serum lipids.[36,37]

Would treatment of patients with chronic essential hypertension with those antihypertensive agents with favorable or neutral effects on serum lipids and lipoproteins and other coronary heart disease risk factors result in a lower risk of coronary heart disease in 10 to 20 years compared with the traditional use of diuretics and β-blockers that are known to have an adverse effect on serum lipids and lipoproteins? If one assumes that alterations of a risk factor alter the risk of coronary heart disease, that alterations in lipid concentrations resulting from the effects of drugs have the same prognostic significance as those occurring naturally and that the effects of the antihypertensive drugs observed in short-term studies can be extrapolated to a lifetime of therapy, then such a hypothesis would seem plausible. Table 1 shows the potential coronary heart disease risk of a 50-year-old white man at various blood pressure and cholesterol levels when treated with a regimen of antihypertensive drugs with unfavorable, neutral or favorable effects on serum lipids.

The adverse changes in serum lipid levels that occur with diuretics and β-blockers are significant and long term—up to six years and possibly longer—as shown by the MRFIT study if correction is made for diet, weight loss, exercise or other factors that influence serum lipid levels.[8] Those patients treated with diet plus diuretics or diet plus β-blockers had significantly greater adverse effects on serum lipid and lipid subfraction levels, compared with those patients treated with diet alone. An attempt should be made to keep the ratio of total cholesterol to high-density-lipoprotein cholesterol to less than 4.0 to reduce the risk of coronary heart disease.

TABLE 1.—*Projected Statistical Risk of Coronary Heart Disease (CHD) Based on Total Cholesterol and Diastolic Blood Pressure (DBP) Levels.**

Antihypertensive Therapy	*Patient Profile*		*Risk of CHD*	
	DBP, mm of mercury	*Cholesterol, mg/dl*	*Years*	*Percent*
Baseline	93	221	5	3.0
			20	16.5
Drugs with unfavorable effect on lipids†	88	239	5	3.0
			20	16.5
Drugs with neutral effects on lipids‡	88	221	5	2.5
			20	14.0
Drugs with a favorable effect on lipids§	88	203	5	2.0
			20	12.0

*Assumes a 5-mm-of-mercury reduction in diastolic blood pressure and an 8% increase, decrease (18 mg/dl) or no change in total cholesterol levels in a 50-year-old white man.

†Diuretics, β-blockers, methyldopa, reserpine.

‡Angiotensin-converting enzyme inhibitors, calcium channel blockers, β-blockers with intrinsic sympathomimetic activity, hydralazine hydrochloride, minoxidil.

§Prazosin, clonidine, guanabenz.

There are numerous nondiuretic and non-β-blocker antihypertensive drugs that are not only as effective but are more effective than diuretics and β-blockers in the treatment of essential hypertension and have fewer clinical symptomatic side effects.[16] In addition, studies now indicate that clinical adverse effects caused by both diuretics and β-blockers are significantly greater than originally reported.[7] The α-blocker prazosin, the central α-agonists clonidine and guanabenz, the calcium blockers nifedipine, diltiazem and verapamil and the angiotensin-converting enzyme inhibitors captopril and enalapril are effective as initial and as monotherapy in 60% to 70% of patients with mild essential hypertension with excellent blood pressure control and favorable effects on coronary heart disease risk factors. These agents if titrated slowly and in low doses are well tolerated and cost-effective.

Although some consider it too early for a drastic change in our recommended therapy for hypertension, it would be prudent and advisable, if diuretics are selected, to use lower doses (hydrochlorothiazide, 12.5 to 25 mg per day) for hypertension. This dose achieves 80% to 100% of the maximum blood pressure reduction.[38] In addition, the indiscriminate use of β-blockers for treating hypertension should be seriously questioned. Initial treatment and serial metabolic indices (lipids, lipid subfractions, lipoproteins, glucose and so forth) should be monitored in all patients receiving antihypertensive pharmacotherapy. Adverse changes in coronary heart disease risk factors must be recognized and treated appropriately, the offending agent stopped and alternate antihypertensive agents should be selected.

It is quite possible that the traditional stepped-care approach to the management of essential hypertension using diuretics and β-blockers as first-line initial monotherapy may go the way of enemas, laxatives, phlebotomy and leeches for the treatment of cholera and radiation therapy for the treatment of goiters and acne. Agents such as prazosin, clonidine, guanabenz, nifedipine, diltiazem, verapamil, captopril and enalapril could become the initial drugs of choice in patients with essential hypertension. Large-scale clinical trials are needed to answer these questions.

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The Pathogenesis and Prevention of Diabetic Nephropathy

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

LLOYD H. SMITH, JR, MD:* *When insulin was discovered, more than 60 years ago, it was at first assumed that diabetes mellitus would no longer be a lethal disease. The treatment would be simply by hormone replacement and would be as successful as the treatment of myxedema by thyroid extract. This, of course, has not turned out to be the case. Diabetic patients, although rarely dying of ketoacidosis, are heir to severe complications in the vascular system, often with devastating results in the heart, retina, nerves and kidneys. In this conference Dr Rodney Omachi will review for us the current concepts of how diabetes injures the kidney and what can be done to prevent, or at least to slow, this process.*

RODNEY OMACHI, MD:† Diabetic nephropathy is now, or soon will be, the most frequent cause of end-stage renal disease in the United States. It accounted for about 25% of all new cases of end-stage renal disease as of 1980, when its incidence was increasing and approaching that of all types of glomerulonephritis combined.[1] Patients with insulin-dependent diabetes have a 40% risk for diabetic nephropathy, which most frequently develops after 10 and before 20 years of diabetes. The yearly incidence declines after 20 years, suggesting that susceptibility to this complication is predominantly in this subset of about 40% of the total population.[2] In patients with maturity-onset diabetes, the prevalence of a urine protein level of over 500 mg a day reaches 35% after 20 years. Although these older patients often die of diabetic complications other than uremia,[3] the highest incidence of end-stage diabetic nephropathy is in the 45- to 64-year age group, and the incidence in the over-65-year age group is twice as high as in the 14- to 44-year age group.[1] Our experience at the University of California, San Francisco, confirms this high incidence and this age distribution. Of 22 consecutive cases of diabetic nephropathy presenting with end-stage renal disease, the onset of our patients' diabetes was before age 30 in a third, between ages 30 and 40 in a third and over age 40 in a third. The median age at initiation of dialysis was 58. Life-table analysis showed a 50% mortality after three years on dialysis, which is disappointing but better than the results generally reported. In short, diabetic nephropathy is a frequent cause of renal failure and strikes patients of all ages. Fortunately, in the past five years there have been major advances in our understanding of the pathogenesis of diabetic nephropathy and the development of a potential both to prevent it and to arrest its progression.

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The Stages of Diabetic Kidney Disease

Figure 1 is a map of the two routes that patients with diabetes currently follow, with an increasing duration of diabetes from left to right and increasing severity of renal involvement from top to bottom.[4,5] Microalbuminuria is defined as albuminuria that is below the level of routine chemical detection—about 150 mg per day—but abnormal and detectable by more sensitive immunoassay. Renal function is abnormal at the onset of diabetes but is supranormal rather than impaired. Increased glomerular capillary pressure and glomerular filtration rate accompanied by microalbuminuria occur during the severe hyperglycemia of uncontrolled diabetes and partially abate with routine control of the hyperglycemia. By the time diabetes has been diagnosed, the kidneys are enlarged but the glomeruli are histologically normal. After only three to five years of diabetes, mild diabetic histologic changes have occurred in virtually all persons with diabetes. Glomerular capillary basement membranes are abnormally thick, and the glomerular mesangium is increased in area. These changes are milder but similar in kind to the changes of overt diabetic nephropathy shown in Figure 2. Microalbuminuria may be precipitated by exercise or severe hyperglycemia but is not present at rest. Most patients with insulin-dependent diabetes continue with these mild changes without increasing severity, but in a substantial minority the disorder progresses to a stage called incipient diabetic nephropathy. These patients have no measurable histologic progression on renal biopsy, but certain renal functional features

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ABBREVIATIONS USED IN TEXT

Ig = immunoglobulin
PG = prostaglandin

indicate their high risk of progressing to overt diabetic nephropathy and also appear important in the pathogenesis of overt nephropathy. These functional features are a more extremely elevated glomerular filtration rate, microalbuminuria at rest and a tendency to arterial hypertension. Intensive insulin therapy in different studies does or does not result in reversal of the hyperfiltration and microalbuminuria, but the

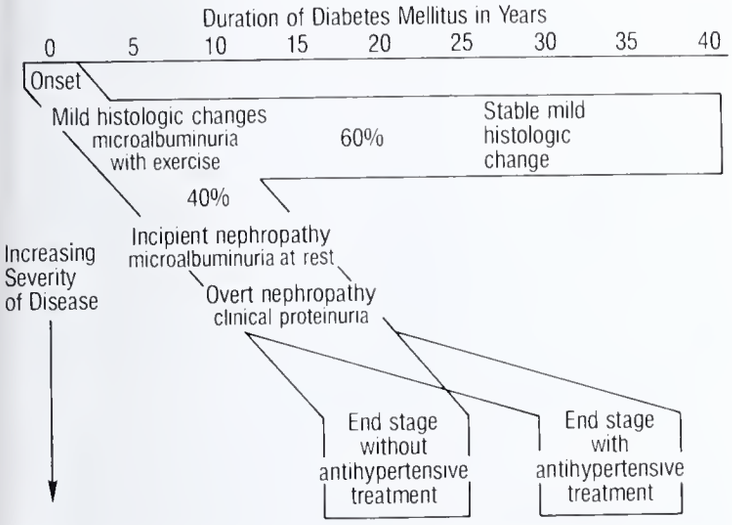

Figure 1.—A map of the renal courses which insulin-dependent diabetics currently follow.

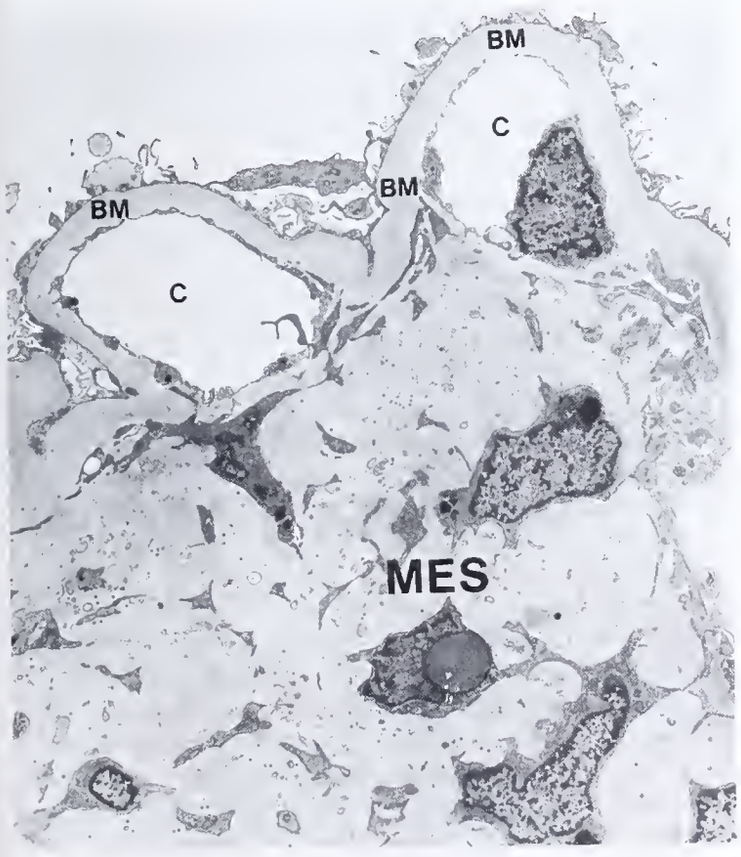

Figure 2.—Overt diabetic nephropathy. An electron micrograph (× 5,000) of a typical glomerulus showing a greatly expanded mesangial area **(MES)** encroaching on the capillary lumina **(C)**, and threefold thickening of the peripheral capillary basement membrane **(BM)**. The capillary lumen is separated from the mesangium only by fenestrated endothelium and not by basement membrane.

natural history with routine diabetic care is progression within ten years to overt diabetic nephropathy, defined operationally as persistent clinical proteinuria in the absence of evidence of other renal disease. Overt nephropathy is characterized by expansion of the mesangium to occupy more than 37% of the total glomerular area, illustrated in Figure 2, and by inexorable loss of renal function, with half of the patients reaching end stage within ten years. The rate of this progression is not slowed by intensive control of diabetes but is slowed by control of secondary hypertension, which becomes overt at this stage. The evidence for these stages in diabetic kidney disease has been developed in insulin-dependent diabetes mellitus, but I will mention its applicability to non-insulin-dependent diabetes. In each stage there is an interplay between the metabolic abnormalities of diabetes and the resultant hemodynamic abnormalities in the kidneys that, at the critical stage of incipient nephropathy, can result in self-perpetuating renal damage.

The mechanism of proteinuria differs at each stage in this map.[6] Microalbuminuria occurs at onset (associated with extreme hyperglycemia), with mild histologic changes (precipitated by exercise) and with incipient nephropathy at rest. This microalbuminuria is initially accompanied by a proportional increase in renal clearance of immunoglobulin (Ig)G. This conforms with microalbuminuria being due to increased glomerular pressures and fluxes rather than intrinsic changes in the glomerular membrane. With increasing microalbuminuria at rest, proteinuria then becomes selective for negatively charged albumin, consistent with a loss of the negative ionic charge on the glomerular filtration barrier. In human and experimental diabetes, glomeruli show decreased anionic sialic acid and heparan sulfate incorporation into glycoproteins and proteoglycans. Therefore, in the stage of incipient nephropathy the hemodynamically induced microalbuminuria may become compounded by this biochemical membrane defect. Finally, when renal failure develops, increased leakage of IgG and other large molecules into the urine occurs, consistent with the development of isolated membrane defects. At least in part, this accounts for the appearance of massive and nonselective proteinuria as a terminal event.[7]

The Kidney at Onset of Diabetes

When diabetes mellitus is first diagnosed, the glomerular filtration rate is already elevated 30% to 40% above normal.[8,9] This is not due to any increase in extracellular fluid volume.[8] Plasma glucagon and growth hormone levels are often elevated, and infusion of these hormones in normal persons results in increased glomerular filtration, but these hormones are not the major mediators of this effect of hyperglycemia. About half of this increase in the glomerular filtration rate reverses with only eight days of near-normal metabolic control, despite no change in plasma glucagon or growth hormone levels.[9] The remaining hyperfiltration may be a result of a 30% increase in kidney size, which does not reverse with short-term metabolic control, although in diabetic rats the hypertrophy is prevented by tight control.[10]

Glomerular prostaglandins appear to be major mediators of the hyperfiltration of diabetes. Isolated perfused rat kidneys respond to severe increases in perfusate glucose levels with immediate and sustained vasodilatation and increased glomerular filtration. This response is prevented by blockade

of prostaglandin synthesis.[11] Glomeruli and cultured mesangial cells isolated from diabetic rats produce increased amounts of prostaglandin (PG) E_2, and urinary excretion of PGE_2 is increased in diabetic rats. In patients with short-term diabetes, inhibition of prostaglandin synthesis by salicylate reverses the increased glomerular filtration.[12]

Microalbuminuria, as a consequence of hyperfiltration, is present before insulin treatment and abates after only a few days of insulin therapy.[13] Exercise increases the microalbuminuria, but even this increase is reversed by insulin treatment for two weeks.[14]

Mild Diabetic Changes

In human diabetes, peripheral capillary basement membrane thickening and expansion of mesangial matrix are absent at the onset of diabetes but are discernible after only two years. After five years of diabetes, basement membrane thickness is increased by 30%.[15] Nondiabetic identical twin offspring of patients with diabetic nephropathy have glomerular basement membranes of normal thickness, whereas the thickness of quadriceps muscle capillary basement membranes in nondiabetic and diabetic twins exceeds normal in about a third of both groups. Glomerular basement membranes are thickest in those persons with diabetes with thickened muscle capillary basement membranes.[16] Whether overt diabetic nephropathy is more likely to develop in these patients is not known. Thickening of glomerular basement membranes and mesangial matrix also occurs in most patients with diabetes due to pancreatic disease[17] and in rats, dogs and monkeys with experimentally induced diabetes. Moreover, thickening of glomerular basement membranes and mesangial matrix as well as hyalinosis of both afferent and efferent arterioles, specific for diabetes, will develop in nondiabetic kidneys transplanted into diabetic recipients.[18] Studies so far have reported an absence of these changes in renal transplants done along with successful pancreatic transplantation.[19] Therefore, the diabetic state is necessary and sufficient for the development of these mild histologic changes, but genetic factors may modulate the degree of change.

The mechanism of these histologic changes has been elucidated in rats with streptozocin-induced diabetes. The renal pool size of uridine triphosphate and diphosphate glycosides is moderately increased.[20] These are substrates used in the synthesis of glycoproteins, which are the major components of glomerular capillary basement membrane and mesangial matrix. A variety of enzymes involved in glomerular protein glycosylation have been shown to be present in increased activity,[21] and glycosylation of glomerular basement membrane and mesangial protein has been shown to be increased.[22] After six to eight months of experimental diabetes, glomerular basement membrane thickness increases by 50% and the volume of mesangial matrix is increased. In part, the mesangial thickening and increase in mesangial cells may also be a reflection of mesangial injury resulting from changes in glomerular hemodynamics. As shown in Figure 2, the mesangium is separated from the glomerular capillary lumen only by the endothelium and not by glomerular basement membrane, and plasmic flow carries circulating macromolecules through mesangial channels.[23] IgG, IgM and C3 enter the mesangium in this way in experimentally induced diabetes. After pancreatic islet cell transplantation, their deposition is rapidly reduced, and subsequently mesangial thickness returns toward normal.[24]

In cases of diabetes, kidneys with mild histologic changes are characterized functionally by progression of the hyperfiltration and hypertrophy present at diagnosis of diabetes. Poor metabolic control is positively correlated with higher glomerular filtration,[25] which is positively correlated with greater renal size.[26] Intensive metabolic control for one year substantially reverses the hyperfiltration but not the renal hypertrophy, so that a return to conventional insulin therapy immediately results in the return of hyperfiltration.[27] In contrast to the situation at the onset of diabetes, conventional insulin therapy at the stage of mild histologic changes does not prevent microalbuminuria with levels of exercise that do not cause microalbuminuria in normal controls.[14] Microalbuminuria apparently does not develop in children with exercise, in contrast to the case with adults, after a comparable duration of diabetes.[28] Perhaps this is related to the observation that, in juvenile-onset diabetes, the prevalence of diabetic nephropathy correlates better with attained age than with the duration of diabetes.[2] This suggests that some process resulting in microalbuminuria with exercise and necessary for the development of overt nephropathy usually begins with puberty.

Incipient Diabetic Nephropathy

Microalbuminuria at rest of a level greater than 15 to 30 μg per minute, unlike exercise-induced microalbuminuria, develops in only a minority of persons with insulin-dependent diabetes and indicates, with high sensitivity and specificity, that overt diabetic nephropathy will develop within 10 to 14[4,5] years with conventional diabetic therapy. In maturity-onset diabetes the test is less specific, perhaps due to other conditions such as congestive heart failure and urinary tract infection, with clinical proteinuria developing in only 22% within nine years.[3]

Microalbuminuria at rest, despite its grave prognosis, does not correlate with more severe histologic changes on renal biopsy. Glomerular basement membrane thickness, percent mesangial area and peripheral capillary wall area versus mesangial capillary wall area are no different in patients with microalbuminuria at rest from those in patients without microalbuminuria matched for age and duration of diabetes.[29] This absence of correlation is particularly striking because percent mesangial area correlates well with the presence of overt diabetic nephropathy. The still mild histologic changes seem to be only a necessary background on which overt nephropathy develops.

Certain functional characteristics associated with microalbuminuria at rest appear to trigger the progression to overt diabetic nephropathy. Early in the development of microalbuminuria, at levels below 70 μg per minute, glomerular filtration is more extremely elevated as compared with the mild hyperfiltration in patients of similar duration of diabetes and age who do not have microalbuminuria and do not progress to have clinical proteinuria.[5] In patients with more severe microalbuminuria and then clinical proteinuria, glomerular filtration falls back to normal and then subnormal. Arterial pressure is also significant—though not in the overtly hypertensive range—in the group with microalbuminuria.[5,30]

Several observations suggest that metabolic control of diabetes is a major factor in whether incipient and then overt

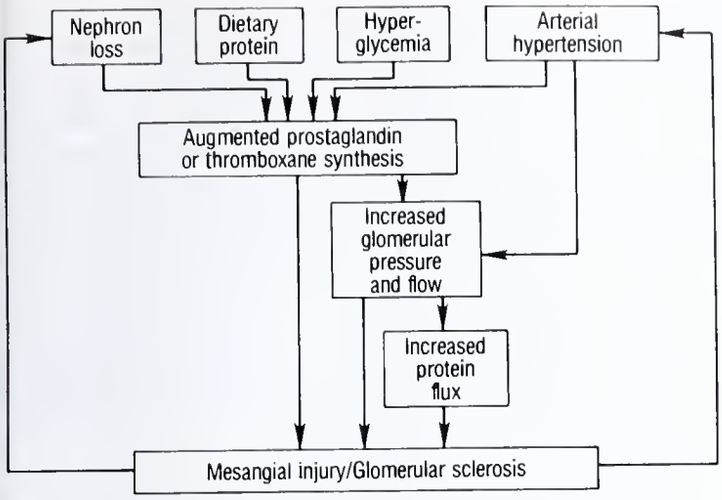

Figure 3.—Proposed mechanism resulting in glomerular sclerosis.

diabetie nephropathy will develop. As mentioned above, experimental hyperglyeemia in isolated kidneys and in vivo ean produee the hemodynamie renal ehanges, whieh ean then produee mieroalbuminuria. Patients with mieroalbuminuria on average have higher glyeosylated hemoglobin and mean plasma glueose levels on 24-hour profiles than patients without mieroalbuminuria.[6,30] Moreover, the risk of developing elinieal proteinuria is eonsiderably greater[2] and the duration of diabetes until the development of proteinuria is shorter[31] in patients with more poorly eontrolled diabetes compared with patients with better eontrolled diabetes of similar age and duration of disease. Clinieal proteinuria has also been reported to reverse with panereatie islet transplantation in diabetie rats with unilateral nephreetomy[32] and in two diabetie human kidneys transplanted into nondiabetie reeipients.[33] In some controlled studies, intensive insulin therapy has resulted in rapid reversal of mieroalbumínuria,[6] and this improvement is sustained at least eight months.[34] Another eontrolled study, however, has shown no improvement in mieroalbuminuria with similar striet metabolie eontrol in similar patients followed for one year. This latter study also did not find the reduced glomerular filtration during striet metabolie eontrol reported in other studies, and the patients had lower initial glomerular filtration rates than might be expeeted.[35] It might be speculated that the patients in the latter study had already experieneed a deeline in their glomerular filtration rate and that the metabolieally influeneed meehanism of glomerular hyperfiltration and microalbuminuria had been lost. This leads us now to consider the nonmetabolie faetors in diabetes that may result in progression of nephropathy.

Role of Hemodynamic Factors

Brenner and eolleagues[36] first presented many of the eoneepts in Figure 3 to explain why ehronic renal failure tends to progress inexorably, even in models of surgieal ablation of renal mass in whieh the remaining nephrons are normal. A loss of nephron mass leads to eompensatory hyperfunetion in the remaining nephrons, which in the short run tends to maintain renal funetion. This sustained single-nephron hyperfiltration, however, or some determinant thereof, appears to be ultimately detrimental to the glomerulus. Glomerular eapillary pressure is determined by intra-arterial pressure and by the ratio of efferent (postglomerular) arteriolar resistance to afferent (preglomerular) resistanee. Hyperglyeemia, dietary protein intake and arterial hypertension, as well as reduced renal mass, result in an increase in single-nephron glomerular filtration and glomerular capillary pressures and flows. This augments the glomerular transcapillary eonvective flux of plasma proteins and is refleeted in the development of mieroalbuminuria in incipient diabetie nephropathy. The plasma proteins thus leaked accumulate in the mesangium by plasmie flow, mentioned above, stimulating proliferation of mesangial cells and matrix and leading to glomerular selerosis. Glomerular hypertension may also cause glomerular injury direetly. The resulting glomerular selerosis eauses progressive arterial hypertension and eompensatory hyperfiltration of the remaining glomeruli, thereby closing a positive feedbaek loop favoring progressive glomerular injury. The theory fits well with the features of incipient diabetie nephropathy mentioned above: extreme elevation in the glomerular filtration rate, elevation in filtration fraction (refleeting increased glomerular capillary pressure), sustained microalbuminuria and often signifieant arterial hypertension. The theory also leads to eertain predictions that have now been tested experimentally in rats made diabetie with streptozoein.

The first prediction is that ehanges in dietary protein will affeet the development of diabetic nephropathy. If diabetic rats are given a high-protein diet, their kidney weight, glomerular eapillary pressure and glomerular filtration rate are higher than in nondiabetic rats on high-protein diets or in diabetie rats on low-protein diets. The most striking abnormality is inereased glomerular capillary pressure due to disproportionate afferent arteriolar dilatation, whieh is absent in the other groups. As predieted, notable progressive albuminuria, mesangial expansion and glomerular selerosis develop in only the diabetie rats on a high-protein diet.[37] Like hyperglyeemia, dietary protein loading increases glomerular filtration in assoeiation with augmented produetion of glomerular prostaglandins and thromboxanes.[38]

Another prediction of the theory is that a reduced renal mass would predispose to the development of diabetie nephropathy. Unilateral nephreetomy plus induetion of diabetes in rats results in the development of mesangial matrix thickening within one year, whereas neither maneuver alone does so.[39] Moreover, sueeessful panereatic transplantation does not result in reversal of the mesangial thiekening in rats with one kidney removed, whereas it does reverse the mesangial thickening that develops after a year in diabetic rats with intact renal mass.[40] Renal prostaglandin synthesis is increased in cases of ehronie renal failure and with dietary protein loading and hyperglyeemia.[41]

The final prediction of the theory is that pharmaeologic normalization of glomerular hemodynamics would prevent the development of diabetic nephropathy. The angiotensin I-eonverting enzyme inhibitor enalapril reduces systemic blood pressure and normalizes the glomerular capillary pressure in diabetie rats on normal protein diets. It also prevents the progressive mild albuminuria and the mild glomerular sclerosis that develops at 14 months.[42]

An alternative interpretation of the above data on the effeets of dietary protein, enalapril and a reduced renal mass on diabetie nephropathy is that they may have effeets mediated direetly by prostaglandin or thromboxane synthesis (or both) rather than through hemodynamie ehanges. Aspirin prevents both the inerease in PGE_2 synthesis and the progressive de-

cline in glomerular filtration rate in long-term diabetes in rats.[43] In some nondiabetic models, recent preliminary reports, so far in abstract only, have dissociated a single-nephron glomerular filtration rate from the development of glomerular sclerosis. In experimental glomerulonephritis in rats, high protein intake does not increase the glomerular filtration rate but does result in increased glomerular prostaglandin and thromboxane synthesis and increased proteinuria. In this model, enalapril reduces glomerular prostaglandin and thromboxane synthesis[38] and reduces proteinuria but does not reduce the glomerular filtration rate.[44] Accelerated glomerular sclerosis develops in spontaneously hypertensive rats on a high-protein diet. Enalapril reduces the glomerular sclerosis without reducing the glomerular capillary pressure and with an increase in the glomerular filtration rate and blood flow. This beneficial effect of enalapril is not simply due to reduced arterial pressure. Hydralazine also reduces arterial pressure and increases the glomerular capillary pressure, glomerular filtration rate and blood flow but increases glomerular sclerosis in this model.[45]

Hyperglycemia, dietary protein, arterial hypertension and loss of renal mass thus all appear to predispose to the development of progressive glomerular sclerosis experimentally through changes either in glomerular hemodynamics or in prostaglandin or thromboxane synthesis. The above findings have now been found to have clinical relevance in overt diabetic nephropathy, a stage in which manipulation of factors other than metabolic control appears promising.

Overt Diabetic Nephropathy

Once persistent proteinuria develops due to diabetic nephropathy, conventional treatment cannot prevent a subsequent inexorable loss of renal function.[2] The structural feature best correlating with overt diabetic nephropathy is mesangial enlargement. In one series of patients with insulin-dependent diabetes studied by renal biopsy, when mesangium accounted for more than 37% of total glomerular volume, persistent proteinuria and hypertension were invariably present. Moreover, the absolute peripheral capillary filtering surface increased with mild mesangial expansion, was greatest when mesangium accounted for 27% to 37% of the total area and then fell off considerably when the mesangium was more than 37%.[29] Thus, at this stage hypertension and a reduction in surface area for glomerular filtration predispose to inexorable progression.

Prospectively, intensive metabolic control has been shown effective in preventing deterioration in renal function in only one study, in patients with background retinopathy with a normal creatinine clearance not characterized as to proteinuria.[46] In one retrospective study, the duration of persistent proteinuria until the development of elevated creatinine concentrations was correlated with a median postprandial blood glucose concentration, but once the serum creatinine level was elevated, a decay in renal function was not correlated with the blood glucose.[31]

There is good evidence that controlling hypertension effectively preserves renal function in patients with diabetic nephropathy. In retrospective studies, the rate of decay in renal function varies greatly among patients, is constant with time in any one patient and is faster in patients with persistent hypertension[31] and in those whose hypertension is less well controlled.[47] Statistically significant increases in blood pressure are present even in incipient diabetic nephropathy, and overt hypertension is present in most insulin-dependent patients with overt nephropathy with a normal serum creatinine level.[48] Aggressive antihypertensive treatment results in a decrease in proteinuria and slowing of the average rate of decline in glomerular filtration rate from 0.84 to 1.23 ml per minute per month without treatment to 0.39 to 0.49 ml per minute per month with treatment both in historically controlled[49,50] and prospective randomly controlled[51] studies. At these rates, the time required for deterioration of the glomerular filtration rate from 110 ml per minute to 10 ml per minute would be 7 to 10 years without treatment and 17 to 23 years with aggressive treatment of hypertension.

It is not established at present which antihypertensive agents will best preserve renal function in diabetic nephropathy. In the studies cited above, metoprolol, hydralazine and a diuretic were used. Thiazide diuretics should probably have a major role in that the hypertension of early diabetic nephropathy is associated with sodium retention and increased pressor responsiveness to infused angiotensin and norepinephrine, and all of these are reversed by thiazides.[52] Clonidine decreases plasma norepinephrine levels and, at least in rats with three fourths of their kidney mass removed, is effective in retarding the progression of renal failure and proteinuria.[53] Clonidine also is effective in relieving some cases of diabetic diarrhea.[54] Hydralazine should perhaps be replaced by enalapril if the above findings in hypertensive rats on high-protein diets[45] can be applied to diabetic nephropathy. As mentioned above, the use of enalapril has resulted in better preservation of renal function in experimental diabetes.[42] This has been attributed perhaps to inhibition of angiotensin II-mediated uptake of macromolecules and disruption of their clearance from the mesangium[55] or perhaps to inhibited prostaglandin or thromboxane synthesis.[42] Captopril, another inhibitor of angiotensin-converting enzyme, has been reported in low doses to decrease proteinuria in some cases of azotemic diabetic nephropathy.[56] High-dose captopril should probably be avoided due to a slight risk of its inducing membranous glomerulonephritis superimposed on diabetic nephropathy.

One small study suggests that dietary protein restriction may be efficacious in human diabetic nephropathy and in experimental diabetes. Ten patients with chronic renal insufficiency from diabetes were studied on 1 to 1.5 grams per kg per day protein intake and then on 0.6 grams per kg per day. The urine protein level decreased by 3% to 77% at one month and by 22% to 83% at three months, the serum albumin level remained normal or increased to normal and the serum creatinine level and creatinine clearance remained stable for a mean of 6.7 months follow-up.[57]

Conclusions

In its early stages, diabetic nephropathy is characterized by mild histologic changes and striking functional changes that are caused by the metabolic abnormalities of diabetes and can be ameliorated by strict metabolic control. Within about ten years, microalbuminuria at rest appears in a substantial minority of persons with diabetes and, with conventional insulin therapy, is followed within ten years by overt diabetic nephropathy. Intensive insulin therapy may or may not reverse the microalbuminuria and the associated glomerular

hyperfiltration. Overt diabetic nephropathy initiates a vicious cycle, and at this stage metabolic control is less influential than treatment of arterial hypertension in determining the subsequent decline in renal function. Experimental evidence has accumulated supporting the mediating role of glomerular hemodynamics or prostaglandin or thromboxane metabolism in the progression of diabetic nephropathy. Results of clinical trials on the effects of long-term intensive insulin therapy in patients with microalbuminuria and on the effects of inhibitors of angiotensin-converting enzyme, dietary protein restriction and perhaps prostaglandin or thromboxane inhibitors are likely to revolutionize the prevention and treatment of diabetic nephropathy.

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Epitomes

Important Advances in Clinical Medicine

Pediatrics

The Scientific Board of the California Medical Association presents the following inventory of items of progress in pediatrics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in pediatrics that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pediatrics of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Hepatitis B Vaccine

THERE ARE SEVERAL viral agents that may infect the liver in humans and produce hepatitis. These include hepatitis A, or infectious hepatitis, hepatitis B (HBV), referred to in the past as either serum hepatitis or Australian-antigen hepatitis, and a third form produced by the interaction of HBV and another small virus called the δ-particle, which by itself is unable to cause disease. In addition, there are cases of hepatitis that are not A, not B and not δ for which specific laboratory methods of identification are not yet available. These are diagnosed by exclusion and called "non A-non B."

The only vaccine currently available is for HBV; it is a preparation of virus surface particles purified from human plasma and inactivated by a procedure designed to render noninfectious all known types of virus including that which causes the acquired immunodeficiency syndrome, human T-lymphotropic virus type III. Studies with the vaccine have shown that antibody is produced in 80% or more of those who receive the series of three doses and that adequate antibody levels correlate with protection from infection. The vaccine is recommended only for selected segments of the population.

The behavior and frequency of HBV infection varies in different parts of the world and in different subgroups within a country. In China, Southeast Asia and parts of South America and Africa, 5% to 15% of the population acquire the virus at birth or shortly thereafter and have a high risk of chronic hepatitis, cirrhosis or primary hepatocellular carcinoma. Infection in Western Europe and Australia occurs principally among adults and has a much lower prevalence and less of a risk for sequelae. In the United States, the prevalence of HBV infection is about 5% among the general population, but much higher and rapidly increasing among sexually promiscuous young adults who use intravenous drugs or live under crowded, unsanitary conditions. It is estimated that 6% to 10% of these groups become ongoing carriers, that 25% of the carriers progress to have cirrhosis and many die of chronic liver disease or cancer each year.

HBV prophylaxis is available as immediate but temporary passive immunization in the form of a high-titer-antibody immunoglobulin called hepatitis B immunoglobulin or regular pooled immunoglobulin containing a lower titer of antibody to HBV (regular immunoglobulin) and the active long-term protection obtained from hepatitis B vaccine. The immunoglobulin is used for postexposure protection and the vaccine for both preexposure and postexposure prophylaxis. Adverse reactions with the vaccine are few and consist mainly of pain at the site of inoculation. There are insufficient data to predict the total duration of antibody persistence but it appears to be in excess of four years.

Vaccine Administration

Primary immunization includes three doses of vaccine given intramuscularly, with the second and third following the first by an interval of one and six months, respectively. Those at significant risk of HBV infection who should receive the vaccine include

- Health care workers;
- Users of illicit injectable drugs;
- Contacts of HBV carriers: household, sex partners, institutional;
- Hemodialysis patients, recipients of possibly HBV-infected products;
- Homosexually active men;
- International travelers, others considered at righ risk, and
- Those with accidental percutaneous or sexual exposure (hepatitis B immunoglobulin plus vaccine).

The use of HBV vaccine in newborns delivered of HBV-carrier mothers is discussed in the June 1984 issue of this journal.

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Hepatitis B vaccine: Evidence confirming lack of AIDS transmission—Immunization Practices Advisory Committee (ACIP). MMWR 1984 Dec; 33:685-687

Recommendations for protection against viral hepatitis—ACIP. MMWR 1985 Jul; 34:313-335

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Chlamydia trachomatis in Adolescents

Chlamydia trachomatis is the most common sexually transmitted disease agent, and a young age appears to be an important risk factor related to its genital infections. Prevalence rates for endocervical infection have been reported at between 8% and 22% among adolescent girls attending teen clinics to as high as 37% among those presenting for prenatal care. Although comparable statistics are currently not available, there are indications that chlamydia may be a common infection among adolescent boys as well. Clinical syndromes frequently associated with chlamydial infection include urethritis in males and cervicitis and pelvic inflammatory disease among females.

Infection with *Chlamydia* in patients with pelvic inflammatory disease results in the most serious sequelae—tubal infertility. It has been estimated that a 15-year-old sexually active girl has a risk of 1:8 of pelvic inflammatory disease developing, compared with a risk of only 1:80 in a 25-year-old woman. Yet it is difficult for both patient and physician to recognize chlamydial infections, as patients frequently present with few or no clinical symptoms or signs. A lack of simple, inexpensive and reliable tests has hindered recognition and control of the chlamydial epidemic among adolescents as well. Tissue culture is currently the gold standard of diagnostic tests but requires costly, sophisticated cell culture techniques, does not render an immediate result and is not widely available to most clinicians. Recently less expensive, rapid, nonculture, fluorescent antibody techniques have been introduced. Evaluation of the performance of such tests, however, among populations who do not attend sexually transmitted disease clinics is limited. Among adolescent boys, there is evidence that screening for pyuria in the first-catch urine specimen (10 or more leukocytes per high-power field, spun urine) may be helpful in identifying occult chlamydial urethritis. The rapid nonculture fluorescent antibody techniques appear to be less sensitive in determining chlamydial infection among men (urethra) than among women (endocervix). Such techniques, therefore, are not recommended for screening male patients for chlamydial infection.

In light of our current limited diagnostic capabilities and of the importance of the role of chlamydial infections in infertility, the Centers for Disease Control have made recommendations regarding the screening and treatment of populations considered at high risk for chlamydial infection. All adolescents with the following symptomatic syndromes associated with chlamydia should receive treatment for chlamydial infection: nongonococcal urethritis, mucopurulent cervicitis, pelvic inflammatory disease and epididymitis. Decisions regarding treatment should be made in conjunction with culture results when available. Because mucopurulent cervicitis, pelvic inflammatory disease and epididymitis are also associated with *Neisseria gonorrhoeae* infection, such patients should also receive effective antigonococcal treatment. Sexual contacts of persons with the above clinical syndromes should be evaluated and treated for presumed chlamydial infection. Routine chlamydial screening of asymptomatic adolescent girls, both pregnant and nonpregnant, is recommended using culture (when available) or rapid nonculture fluorescent antibody techniques. Adolescent boys may be screened by culture or by analysis of a first-catch urine specimen, with the knowledge that information on screening asymptomatic young men is limited. While it is anticipated that improved, cost-effective diagnostic capabilities will be available in the future, the importance of *Chlamydia* in the development of infertility among our youth dictates the current recommendations for treatment and screening of sexually active adolescents.

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Adger H, Shafer MA, Sweet RL, et al: Screening for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in adolescent males: Value of first-catch urine examination. Lancet 1984 Oct; 2:944-945

Chlamydia trachomatis infections: Policy guidelines for prevention and control—Centers for Disease Control. MMWR 1985 Aug; 34(3S):53S-74S

Schachter J, Shafer MA: Female adolescents with chlamydia: Tomorrow's candidates for in vitro fertilization? (Editorial). West J Med 1985 Jul; 143:100-101

Shafer MA, Beck A, Blain B, et al: *Chlamydia trachomatis*: Important relationships to race, contraception, lower genital tract infection, and Papanicolaou smear. J Pediatr 1984 Jan; 104:141-146

Intravenous Immune-Globulin Therapy in Pediatric Hematology

INTRAVENOUS IMMUNE-GLOBULIN THERAPY has recently been shown to be useful in managing autoimmune hematologic disorders. The peripheral blood cells—platelets, erythrocytes and neutrophils—in patients with these disorders are coated with antibodies, predominantly immunoglobulin (Ig)G, and are prematurely removed from the circulation by the reticuloendothelial system, primarily the spleen. The mechanism of action of immune globulin given intravenously (IV) has not been elucidated completely. A number of mechanisms have been proposed, but the best studied and perhaps the most important involves the competitive blockade of specific receptors on macrophages and monocytes within the reticuloendothelial system for the Fc region of the IgG molecule, resulting in improved survival of the antibody-coated cells. Fc-receptor function returns to normal, however, in about four weeks and does not explain the prolonged remission seen in some patients following IV immune-globulin therapy. This suggests that other mechanisms such as decreased antibody production may be involved.

Much of the clinical experience with IV immune-globulin therapy for hematologic disorders has been gained in the treatment of children with immune thrombocytopenic purpura. In several studies a significant rise in the platelet count was shown within one week in 75% to 100% of patients with acute and chronic immune thrombocytopenic purpura. In as many as half of the patients the response is sustained but, in many, periodic booster infusions are required to maintain adequate counts. Children, in contrast to adults, have a higher initial increase in the platelet count, a lower incidence of relapse and a longer duration of response. In addition to this disorder, IV immune-globulin therapy has also been used successfully in the treatment of neonatal isoimmune thrombocytopenia, autoimmune neutropenia and Coombs-positive hemolytic anemia.

The optimal dose of IV immune-globulin has not been established. In most studies 0.4 grams per kg per day was infused over four to eight hours for five consecutive days. A dose of 1 gram per kg per day for one to three days has also been effective. Subsequent booster doses are given as needed.

Toxicity has been limited, provided it is given slowly over a number of hours. Headaches have been reported in 20% of patients and occasionally pallor, nausea, fever or chills. The cost of IV immune-globulin therapy is considerable, however, about $70 per gram.

Intravenously given immune globulin clearly is effective in managing immune hematologic disorders, but its precise role in pediatric hematology has not been completely established. Acute immune thrombocytopenic purpura in children is usually a benign, self-limited condition and, under most circumstances, the cost of giving IV immune globulin does not justify its regular use. A more appropriate use of this therapy may be in patients with potentially serious bleeding or as an alternative to splenectomy for some patients.

GREGORY A. THOMAS, MD
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Bussel JB, Goldman A, Imbach P, et al: Treatment of acute idiopathic thrombocytopenia of childhood with intravenous infusions of gammaglobulin. J Pediatr 1985 Jun; 106:886-890

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Karpatkin S: Autoimmune thrombocytopenic purpura. Semin Hematol 1985 Oct; 22:260-288

Hemophilus influenzae Type b Immunization

A POLYSACCHARIDE VACCINE is now available for the prevention of invasive *Hemophilus influenzae* type b (Hib) disease. Vaccine efficacy is estimated at about 90% for children aged 2 to 5 years. The Hib vaccine induces an antibody response that is directly related to the age of the child. Infants respond less frequently and the current vaccine is of no value in children younger than 18 months.

The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and the American Academy of Pediatrics recommend that all children at 24 months of age receive the Hib vaccine. Additionally, children between the ages of 24 and 71 months should be considered for immunization because the vaccine has proved to be safe and effective. Because children aged 2 to 3 years who attend day-care facilities are at higher risk than older children, higher priority should be given to the younger children. The vaccine is not recommended for children older than 71 months or for adults.

Immunizing children aged 18 to 23 months remains controversial. The ACIP recommends that immunization should be considered for children at 18 months of age who are in known high-risk groups, including those attending day-care facilities and children with chronic conditions known to cause an increased risk for Hib disease such as anatomic or functional asplenia (sickle cell disease or splenectomy) and malignant lesions associated with immunosuppression. Children receiving the Hib vaccine at between 18 and 23 months of age may need to be reimmunized 6 to 18 months following the original immunization to ensure protection. Hib and the diphtheria-tetanus-pertussis (DTP) vaccine can be administered simultaneously at separate sites without impairing the immune response to the individual antigens.

Hib immunization is given as a single subcutaneous dose of 0.5 ml. Mild local reactions and low-grade fever may occur, but severe systemic reactions are extremely rare. Simultaneous administration of Hib with DTP does not result in increased reactions to either vaccine. New Hib vaccines are being developed that may provide protection of children younger than 18 months.

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Kayhty H, Karanko V, Peltola H, et al: Serum antibodies after vaccination with *Haemophilus influenzae* type b capsular polysaccharide and responses to reimmunization: No evidence of immunologic tolerance or memory. Pediatrics 1984 Nov; 74:857-865

Peltola H, Kayhty H, Virtanen M, et al: Prevention of *Hemophilus influenzae* type b bacteremic infections with the capsular polysaccharide vaccine. N Engl J Med 1984 Jun; 310:1561-1566

Polysaccharide vaccine for prevention of *Haemophilus influenzae* type b disease—Recommendation of the Immunization Practices Advisory Committee (ACIP). MMWR 1985 Apr; 34:201-205

AIDS in Children

PEDIATRIC acquired immunodeficiency syndrome (AIDS) is a distinct immunodeficiency disorder diagnosed on the basis of epidemiologic, immunologic and virologic data. Currently there are about 200 cases of pediatric AIDS that conform to strict diagnostic criteria established by the Centers for Disease Control. There are probably two to three times that number who have AIDS-related disorders. The total number of AIDS cases in children continues to increase at the same rate as in the adult population.

Epidemiologic factors are the initial indicator for the diagnosis of pediatric AIDS. The following are important risk factors: mothers who use drugs intravenously or who are prostitutes, heterosexual mothers with bisexual husbands, a history of blood transfusions within the preceding five years (this interval may require modification as additional information is obtained), infusion with factor VIII concentrate or an infant born into a family where the father has hemophilia. Persons capable of transmitting the AIDS virus (human T-lymphotropic virus type III/lymphadenopathy-associated virus [HTLV-III/LAV]) are not necessarily ill. Most cases of AIDS from transfusion follow multiple transfusions to a premature or immunocompromised infant.

Infants with AIDS present clinically in a manner similar to patients with other immunodeficiency disorders: recurrent and frequent infections, opportunistic infection, failure to thrive, chronic diarrhea, developmental delay, lymphadenopathy and skin infection are frequent features. Features relatively unique to pediatric AIDS are recurrent parotitis and chronic lymphoid interstitial pneumonitis. The age of onset may vary from the first month of life to as long as five years after exposure. Most infants become symptomatic within the first year.

Laboratory abnormalities include lymphopenia, thrombocytopenia and abnormal chest roentgenograms. In contrast to other immunodeficiency disorders, patients usually have elevated serum immunoglobulins. The T-helper/T-suppressor cell ratio is usually reduced, but unlike that in adult patients may be elevated. This test should not be used to establish a diagnosis. Other immunologic studies show significant impairment of T-cell and B-cell immunity. The most important laboratory test is that of antibody to HTLV-III/LAV. Maternal transfer of immunoglobulin G antibody to HTLV-III/LAV occurs so that testing should be done only after 6 months of age. Isolation of HTLV-III/LAV in an infant younger than 6 months establishes direct infection. Diseases that require ex-

clusion are primary immunodeficiency disorders, especially those associated with adenosine deaminase and nucleoside phosphorylase enzyme deficiency.

Not all children who are antibody-positive have clinical features of AIDS or laboratory abnormalities suggesting immunodeficiency. As the incubation period may exceed five years, these children should be followed carefully for the development of symptoms, immunodeficiency or both. Once the diagnosis is established, appropriate therapy may be instituted, including prophylactic trimethoprim-sulfamethoxazole to prevent *Pneumocystis carinii* pneumonia and intravenous administration of immune globulin to prevent both viral and bacterial infections.

A controversial area of pediatric AIDS relates to public health considerations. There is no evidence of casual spread of HTLV-III/LAV from infected persons to noninfected persons. Direct inoculation of the virus (blood transfusion) or sexual contact is required. Nevertheless, children with AIDS, or those who are antibody-positive but asymptomatic, have been ostracized and prevented from attending school. A physician caring for a child with AIDS may be deeply involved in educating parents, public health agencies, school boards and the public.

ARTHUR AMMANN, MD
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Ammann AJ: The acquired immunodeficiency syndrome in infants and children. Ann Intern Med 1985; 103:734-737

Oleske J, Minnefor A, Cooper R Jr, et al: Immune deficiency syndrome in children. JAMA 1983 May; 249:2345-2349

Rubinstein A, Sicklick M, Gupta A, et al: Acquired immunodeficiency with reversed T4/T8 ratios in infants born to promiscuous and drug addicted mothers. JAMA 1983 May; 249:2350-2356

Long-term Outcome in Infants With a Very Low Birth Weight

WITH THE ADVENT of highly specialized obstetric and neonatal management for high-risk mothers, fetuses and neonates, neonatal mortality has decreased sharply in the past two decades. The major contribution has been the increased survival in very-low-birth-weight infants (less than 1,501 grams). In the period 1950 to 1960, two thirds of the very-low-birth-weight infants died. An infant who weighed less than 1,001 grams at birth had less than a 5% chance of survival. On follow-up, more than half of the surviving very-low-birth-weight infants were found to have significant physical, neurologic and developmental handicaps.

Today many centers report survival rates of 80% in infants with birth weights of from 1,001 to 1,250 grams and 90% in infants weighing 1,251 to 1,500 grams. Are a greater number of very-low-birth-weight infants now surviving only to increase the number of handicapped persons in our society? Apparently not. The infants with birth weights of 1,001 to 1,500 grams, who represent more than 70% of the total very-low-birth-weight group, do well, with less than 10% showing major problems at preschool age. It would appear that perinatal and neonatal management today has proved successful in reducing both mortality and morbidity in infants who weigh more than 1,000 grams at birth.

On follow-up the problems that affected the larger very-low-birth-weight survivors born 25 years ago are now found in the very tiny infants with birth weights of less than 1,001 grams. Recent follow-up programs of infants born in the late 1970s and early 1980s report a high incidence (40% or greater) of major neurodevelopmental handicaps among survivors with birth weights from less than 800 grams. A resurgence of retrolental fibroplasia with severe visual impairment or blindness is reported in more than 10% of the very tiny infants weighing less than 1,000 grams. Because these infants account for less than 0.4% of all live births, however, they represent a very small total number. Mortality has been reduced in these fragile complicated infants but morbidity remains unacceptably high.

The present challenge is the development of perinatal and neonatal management techniques that result in far fewer physically, neurologically and developmentally handicapped children among those born weighing less than 1,001 grams.

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Hack M, Caron B, Rivers A, et al: The very low birth weight infant: The broader spectrum of morbidity during infancy and early childhood. J Dev Behav Pediatr 1983; 4:243-249

Teberg AJ, Wu PY, Hodgman JE, et al: Infants with birth weight under 1500 g: Physical, neurological and developmental outcome. Crit Care Med 1982 Jan; 10:10-14

Human Growth Hormone

DISTRIBUTION of the human growth hormone (hGH), obtained from the pituitary glands of cadavers, was suddenly discontinued in April 1985 following reports that three adults, ages 21 to 34, who received growth hormone treatment beginning in the 1960s had died of Creutzfeldt-Jakob disease, a slow virus infection of the brain. The disease was confirmed by pathologic examination of two patients; the other patient had clinical features of the disease but an autopsy was not done. Only growth hormone-deficient children with hypoglycemia were continued on treatment until a biosynthetic growth hormone was approved by the Food and Drug Administration in October 1985. Although current processing techniques are thought to destroy the virus, it is highly contagious and very resistant to chemical processing. Studies using animals are currently in progress to determine whether the virus can be transmitted in recent growth hormone preparations.

Contamination of hGH preparations with the Creutzfeldt-Jakob virus occurs in several ways: Human growth hormone was previously prepared from as many as 20,000 pituitary glands, yet patients with chronic neurologic diseases were not excluded from the donor population. Because the incubation period of Creutzfeldt-Jakob disease is long, some patients infected with the virus may have died before they were clinically symptomatic, and their infected pituitary glands were included in the donor pool. The incidence of the disease is one per million worldwide; in persons younger than 40, the incidence is .01 per million. Thus, the occurrence of three patients with Creutzfeldt-Jakob disease treated with hGH within one year strongly suggests that the infection was acquired from contaminated hGH preparations.

Although growth hormone-deficient children with hypoglycemia were continued on therapy, no treatment was available for many other growth hormone-deficient children until a biosynthetic human growth hormone (Protropin, Genentech Laboratories, South San Francisco, California) was approved in October 1985. Protropin, synthesized by recombinant DNA techniques using a strain of *Escherichia coli*, contains 191 amino acids identical to hGH plus methionone at the

N-terminal portion of the molecule. In clinical trials with Protropin in growth hormone-deficient children, linear growth rates were comparable to those in children receiving pituitary-derived hGH. Of 84 children treated with Protropin, antibodies to the growth hormone developed in 40%, but this did not interfere with growth except in one child.

The primary indication for treatment with synthetic human growth hormone is growth hormone deficiency shown by subnormal growth hormone response to two provocative tests. Some very short children growing less than 4.5 cm per year but with normal growth hormone levels in response to provocative stimulation have also responded to the use of human growth hormone, but indications for treatment are not well defined. The possible risks and benefits of treatment with hGH in other children with short stature is not yet known.

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Brown P, Gajdusek DC, Gibbs CJ Jr, et al: Potential epidemic of Creutzfeldt-Jakob disease from human growth hormone therapy. N Engl J Med 1985 Sep; 313:728-731

Committee on Growth Hormone Use of the Lawson Wilkins Pediatric Endocrine Society: Degenerative neurologic disease in patients formerly treated with human growth hormone. J Pediatr 1985 Jul; 107:10-12

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Koch TK, Berg BO, De Armond SJ, et al: Creutzfeldt-Jakob disease in a young adult with idiopathic hypopituitarism: Possible relation to the administration of cadaveric human growth hormone. N Engl J Med 1985 Sep; 313:731-733

Current Therapy for Asthma—New Inhalants

INHALATION THERAPY has increased in importance for the treatment of asthma as more effective drugs have become available and newer methods and techniques of delivery have been developed.

Several new β-adrenergic bronchodilator aerosol drugs are available for the treatment of asthma. One of the first β_2-agonists developed for asthma was isoproterenol, which has a short duration of activity and both β_1- and β_2-specific effects. In a search for more selective and longer acting drugs, new agents have been developed by modifying the chemical structure of the basic catecholamine molecule. Isoetharine has a duration of activity similar to that of isoproterenol, but is more β_2-selective. Noncatecholamine inhalants were subsequently developed and include metaproterenol, albuterol, terbutaline and bitolterol. These agents have a somewhat slower onset of action but a much longer duration of activity and greater β_2-selectivity than isoproterenol. Terbutaline, albuterol and bitolterol may be somewhat more bronchoselective and have a longer duration of activity than metaproterenol.

Although the new β-agonists are safer than their predecessors, they can cause adverse effects. Adverse cardiac effects can also be intensified by the concomitant use of theophylline, which can stimulate endogenous catecholamine release. Large doses of inhaled adrenergic agents alone or with theophylline can lead to hypopotassemia, thus greatly increasing the chance of cardiac arrhythmias. Paradoxical increases in airway obstruction and aggravation of hypoxemia reported following isoproterenol sulfate inhalations has not been reported with the newer, more selective agents. Sulfites, used as antioxidants, are present in bronchodilator solutions and have recently been found to cause bronchoconstriction in some susceptible patients with asthma. These substances, however, are not present in metered-dose inhalers or in the individual-dose vials of metaproterenol sulfate solution. With respect to tachyphylaxis, it is felt that the more selective β-agonists can be used for prolonged periods of time without fear of reducing bronchodilator activity.

One third to one half of patients use an improper technique when using metered-dose inhalers, and about 14% to 16% are unable to learn even after careful instruction. A new technologic development uses a spacer attachment consisting of a tube, cone or holding chamber between the actuator of the metered-dose inhaler and the patient's mouth. These devices not only improve delivery of the medication to the lungs and decrease oropharyngeal deposition but, of greatest importance, overcome the need for synchronization between firing the aerosol and inhaling. Large-volume spacers or reservoirs (500 to 1,500 cm) equipped with valves are particularly valuable in this respect. Several types are now available in this country, including Inhal-Aid, InspirEase, Breathancer and Aerochamber. Spacers may be of particular value for administering inhaled corticosteroids by reducing the incidence of oral candidiasis or dysphonia. Beclomethasone, triamcinolone and flunisolide are corticosteroids that can be prescribed for use as aerosols by metered-dose inhaler, as can cromolyn sodium (Intal Spinhaler); the triamcinolone inhaler is available with an attached spacer.

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American Academy of Allergy and Immunology Committee on Drugs: Position statement: Adverse effects and complications of treatment with β-adrenergic agonist drugs. J Allergy Clin Immunol 1985 Apr; 75:443-449

Konig P: Spacer devices used with metered-dose inhalers: Breakthrough or gimmick? Chest 1985; 88:276-284

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Oral Rehydration Therapy for Diarrhea

ORAL REHYDRATION THERAPY for diarrhea uses the principle of glucose-facilitated intestinal absorption of sodium and water to rapidly return a child to a euhydrated state. When successful, rehydration can be accomplished in 6 to 12 hours, obviating the need for parenteral therapy. Recent interest in oral rehydration therapy developed because of the need to find an effective, safe and practical treatment of dehydration associated with cholera in areas where parenteral therapy was unavailable. Use of the World Health Organization (WHO) oral rehydrating solution resulted in a dramatic decrease in mortality. Global acceptance of oral rehydration therapy is slowly evolving. Children have a prodigious capacity to absorb sodium-containing fluid at rates exceeding 15 ml per kg per hour. Intestinal sodium absorption can be facilitated in the presence of 2.0% to 2.5% glucose, but the glucose-linked sodium transport system becomes saturated with glucose concentrations greater than 3%, which may result in increased diarrhea due to intestinal hyperosmolarity. Fasting has a negative effect on sodium and water absorption.

Conventional therapy for diarrhea resulting in dehydration is to withhold oral fluids and replace deficits intravenously over 24 hours. Oral intake of fluids is usually reinstituted with small, frequent feedings of clear liquids followed by diluted formula. While effective and relatively safe, this regimen is empirical, expensive and disregards the capacity of the intestine to absorb fluid and electrolytes despite concomitant stool losses.

In contrast, oral rehydration therapy uses glucose to facilitate intestinal salt and water absorption, deficits being replaced over 6 to 12 hours. Sucrose has been substituted in some regimens because of its universal availability and diminished cost. Its efficacy approaches that of glucose despite dependency on intestinal disaccharidases for hydrolysis. Rice powder that contains glycine plus amylose and amylopectin (which can be hydrolyzed to glucose) will significantly lower stool output and duration of diarrhea when compared with the standard 2% glucose solutions. Homemade sugar-salt solutions are not recommended because of the risk of inappropriate reconstitution.

The WHO oral rehydrating solution contains sodium, 90 mEq per liter; potassium, 20 mEq per liter; chloride, 80 mEq per liter; bicarbonate, 30 mEq per liter, and glucose, 111 mmol per liter. The composition of this solution approximates conventional mixtures used to treat moderate dehydration intravenously except in its glucose concentration. The volume of fluid to be given orally or via nasogastric tube in the first six hours is derived from the estimated percent dehydration (50 to 100 ml per kg), maintenance needs (25 ml per kg per six hours) and projected ongoing losses (12 ml per kg per six hours). Two thirds of the total volume is replaced over four hours with the WHO oral rehydrating solution. The final third is given as free water over the next two hours to allow for renal excretion of excess solute. Alternatively, 100 ml per kg of the WHO solution may be given for four hours, followed by 50 ml per kg of water during the next two hours.

Subsequent oral therapy should provide for maintenance fluid and electrolyte requirements and for anticipated ongoing losses. Use of the WHO oral rehydrating solution during this maintenance phase is not recommended. A solution that contains about 30 to 50 mEq per liter sodium, 20 to 30 mEq per liter potassium and 2% glucose should be used for no more than 24 hours. Return to a non-lactose-containing formula should commence within 24 hours. Breast-feeding should be continued throughout the diarrhea.

Traditionally pediatricians have been warned against rapid rehydration, particularly in children with hypernatremia, to avoid seizures due to intracellular influx of water. Although oral rehydration therapy results in a more rapid fall in serum sodium levels when compared with intravenous therapy, the incidence of seizures is not increased. In one study, the risk of seizures was related to the initial serum sodium concentration rather than to the rate of fall in serum sodium concentration. In addition, the occasional hyponatremia measured after oral rehydration therapy seems to be clinically insignificant. In children with hypovolemic shock, this therapy should only be used after adequate volume expansion with intravenous fluids and when the child is alert enough to cooperate with the regimen. Vomiting is not a contraindication to oral rehydration therapy, as rapid restoration of volume seems to diminish vomiting. Failure can be anticipated if the loss exceeds 10 ml per kg per hour and in children with paralytic ileus, in those with known glucose or sucrose intolerance or when purge rates exceed 10 ml per kg per hour.

Despite these possible obstacles, oral rehydration therapy obviates the need for the intravenous administration of fluids in 75% to 95% of children treated for dehydration. Appropriate use and careful monitoring will assure the safety of oral rehydration, which represents a physiologic, noninvasive and potentially cost-effective alternative approach to the conventional management of diarrhea in childhood.

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Surfactant Treatment of the Respiratory Distress Syndrome

SOON AFTER the identification of dipalmitoylphosphatidylcholine as the principal compound in pulmonary surfactant and the recognition in 1959 that infants who died of the respiratory distress syndrome had abnormal surface properties of the lungs, aerosols of this compound were tried unsuccessfully as treatment for this disorder. In the 1970s, however, a sound scientific basis for treatment with natural surfactant was established in preterm animals. In 1980 the results of the first uncontrolled trial of the use of surfactant prepared from beef lung were published. Since then 15 studies have been published, of which 6 have been controlled, randomized clinical trials. While many of these have shown remarkable responses to surfactant, others have shown no effects, depending on the surfactant chosen for the studies.

Natural pulmonary surfactant is a complex mixture of phospholipids, neutral lipids and at least two classes of surfactant-specific proteins. Surfactant is present in the airways and alveoli as aggregates of various sizes, the most surface active being the largest. These large surfactant aggregates will rapidly absorb to and spread on an air-water interface to establish an equilibrium surface tension of about 25 dynes per cm. On dynamic compression of the surface film, surfactant will lower the surface tension to values less than 10 dynes per cm. These surface properties can be reproduced using carefully resuspended lipid extracts of natural surfactant that contain less than 1% protein. The technique of resuspension is critical to surface behavior, as the composition of a surfactant is less important than the aggregate form of the lipids in suspension. Further, synthetic lipid surfactants can have in vitro properties similar to natural surfactant, yet be inactive in vivo. A surfactant for clinical use is not a traditional single-component pharmaceutical; rather, surfactant is a mixture of compounds whose surface physical properties in vitro may not be sufficient for in vitro function. Responses to a surfactant may be predicted only from the effects on surfactant-deficient premature lungs.

Based on sound experiments in animals, two strategies for clinical trials have been used. In the initial pilot trial, ventilator-dependent infants with severe respiratory distress syndrome were treated with tracheal instillation of suspensions of surfactant in saline. In a number of subsequent trials, workers have tried to prevent the respiratory distress syndrome by treating at-risk infants with surfactant in the delivery room. Infants treated with synthetic surfactants have no immediate improvement in lung function. In contrast, infants treated with animal or human surfactants may have immediate im-

provement in lung function. Following injection of surfactant into the airways of infants with severe respiratory distress syndrome, a surfactant response is characterized by a rapid decrease in oxygen requirements. In some trials, the ventilatory support could be decreased as well. The response was better and more prolonged when treatment was given as soon as possible after initiating ventilation.

Infants treated in the delivery room have a lower incidence and severity of the respiratory distress syndrome than control infants. Overall, treatment at birth decreases the oxygen requirements and ventilator support variables of the treated infants relative to control infants. When the groups treated at birth or after the onset of the respiratory distress syndrome are combined, pneumothorax is decreased from 28% in control to 12% in treated infants, pulmonary interstitial emphysema is decreased from 38% in control to 6% in treated infants and bronchopulmonary dysplasia is decreased from 46% in control to 33% in the surviving treated infants. Mortality was 31% in control infants and 12% in treated infants. Thus, surfactant treatment lowered the incidences of the major pulmonary complications of the respiratory distress syndrome and mortality. Incidences of other nonpulmonary complications of prematurity such as intraventricular hemorrhage, necrotizing enterocolitis or severe retinopathy of prematurity either were unchanged or decreased numerically but not statistically.

Surfactant seems to be a major advance in the treatment of the respiratory distress syndrome. Surfactants tested to date have been "homemade" and are not licensed for clinical use. Standardized surfactant preparations are being evaluated in clinical trials for licensure by the Food and Drug Administration (FDA). At present, a physician can treat infants only by preparing a surfactant and obtaining the necessary FDA permission for experimental drug use.

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Editorials

A Forum to Discuss an Important Subject

ELSEWHERE IN THIS ISSUE is what the editors hope will be just the beginning of a forum to discuss the "Aim of American Medicine Within the Constraints of Today's Society." American medicine is enjoying unprecedented technologic success, while at the same time it is undergoing unprecedented stress. In many ways the stresses now seem to be taking precedence over the successes, at least as far as the medical profession as a whole is concerned. And, surprising though it may be, there seems to be no real consensus or agreement, within or without the profession, about just what should be the basic aim of the medical profession in today's changing social, economic, political and even technologic health care environment. Clearly, as a nation we are entering a period of social transformation that is as yet poorly understood, and just as clearly health care is in the forefront of much that is taking place in the larger environment.

Success and sometimes even survival in any unsettled, stressful or even hostile situation often depend on whether there is a clear purpose and a firm resolve. What was formerly a friendly and supportive environment for medicine and the medical profession is now not always so friendly or supportive. As is already pointed out in the forum, the time-honored and well-proved internal constraints within the medical profession must begin to find ways to work within (or perhaps even to change) the external constraints being imposed by society. This will not be easy, but it will be easier if there can be agreement on what should be the aim of American medicine and if there can be a firm resolve within the profession to achieve that agreed-upon aim. The forum will have served its purpose if it initiates a discussion of this important subject.

MSMW

The Pathogenesis and Prevention of Diabetic Glomerulopathy

SCLEROSING GLOMERULOPATHY develops in approximately 40% of patients with diabetes mellitus. This life-threatening complication becomes clinically manifest a decade or more after the onset of the diabetes and is heralded by the development of persistent proteinuria. Glomerular morphology is altered by an expansion of the extracellular matrices of both the mesangium and the peripheral basement membranes of the glomerular capillary loops.[1] In addition, the functional properties of the glomerular filter exhibit increasing derangement. Progressive impairment of the size-selective properties of the filtration barrier results in increased transmural shunting into Bowman's space of large plasma proteins, leading ultimately to nephrotic-range proteinuria.[2] Simultaneously, the remarkable ability of the glomerular capillary wall to function as a high-capacity ultrafiltration membrane is compromised. Either a reduction of hydraulic conductivity or progressive curtailment of the surface area available for filtration (or a combination of these factors) results in a progressive loss of ultrafiltration capacity by the glomerular capillaries. The rate at which glomerular ultrafiltrate is formed declines predictably, leading eventually to end-stage renal disease.[3]

As discussed by Omachi elsewhere in this issue, diabetic glomerulopathy has emerged as the leading discrete cause of end-stage renal failure in the Western world. During the past decade a substantial investigative effort has been joined to ameliorate its progressive course. Effective control of the arterial hypertension that invariably complicates diabetic glomerulopathy has been shown to slow the inexorable decline in the glomerular filtration rate. Control of hypertension, however, does not arrest, much less reverse, progressive glomerular capillary wall dysfunction.[4,5] Even more ambiguous have been the results of attempts to normalize chronic glycemia by the use of continuous subcutaneous infusion of insulin. This approach has resulted in little or no beneficial effect on progressive glomerular capillary dysfunction in patients with established diabetic glomerulopathy.[6,7] Accordingly, investigations have been intensified to identify a preclinical or occult stage of preproteinuric diabetic glomerulopathy. The hope is that early treatment of latent glomerular capillary dysfunction might prevent the inevitable downhill course that follows in the wake of persistent proteinuria.

A possible precursor to overt proteinuric glomerulopathy in diabetes is the finding that the glomerular filtration rate is sometimes elevated to supernormal levels in patients with type I diabetes of recent onset.[8,9] Since first demonstration of this phenomenon 30 years ago, it has been shown that glomerular hyperfiltration may be accompanied also by a subtle increase in the urinary albumin excretion rate that is not measurable by conventional techniques for detecting proteinuria.[10] Using a sensitive radioimmunoassay, it has been found that healthy nondiabetic subjects excrete albumin in their urine at rates of up to 15 μg per minute. Among persons with diabetes of short duration, by contrast, a proportion excrete immunoassayable albumin at rates below those detectable by conventional techniques (approximately 100 μg per minute) but in excess of 15 μg per minute.[10] To distinguish this phenomenon from overt proteinuria, it has been termed microalbuminuria. Because it has been associated with the most striking degrees of hyperfiltration, it is inferred that an underlying elevation of either the glomerular perfusion rate or pressure leads not only to enhanced formation of filtrate, but also to an increase in transglomerular albumin filtration.

In light of these abnormalities early in the course of diabetes, it has been proposed that either glomerular hyperfiltration per se, an underlying glomerular capillary hyperperfusion or hypertension, an associated increase in traffic of proteins across the glomerular capillary wall or some combination of these factors is the forerunner of sclerosing glomerulopathy in diabetes.[11] This hypothesis is lent credence by observations in rats with streptozocin-induced diabetes. As in humans, newly diabetic rats with moderate hyperglycemia have elevated glomerular filtration rates. Micropuncture studies have shown the diabetic state to be associated with a fall in resistance of cortical microvessels, with the result that

both glomerular capillary perfusion rate and pressure become elevated, thereby accounting for the increased flux of water across glomerular capillaries.[12] Moreover, glomerular ultrafiltration pressure and, hence, nephron glomerular filtration rate can be elevated even further in diabetic rats by surgical reduction of the renal mass or by a diet rich in protein (50%).[13,14] The increment in glomerular capillary perfusion rate and pressure is followed by heavier proteinuria and more severe glomerulosclerosis than observed in diabetic rats with a normal complement of nephrons and fed conventional rat chow (12% protein). The notion that persistent elevation of glomerular perfusion rate, pressure or both is implicated in the genesis of an accelerated sclerosing glomerulopathy is supported by the protective effect of measures that prevent glomerular hyperemia and hypertension in these rodents. Lowering glomerular capillary perfusion pressure by either partial constriction of the renal artery with a clip[15] or the administration of an angiotensin-converting enzyme inhibitor[13] or by restriction of dietary protein intake[14] largely prevents the development of proteinuria and the histopathologic damage found in animals not so protected.

The precise cause of the altered renal vasomotion that attends the diabetic state has yet to be determined. Hyperglycemia per se or elevated levels of vasodilator glucoregulatory hormones such as glucagon and growth hormone may be implicated. There are in the diabetic state also abnormalities of production and activity of several vasoregulatory hormones that are not directly related to glucose metabolism. The renin-angiotensin system, thought by many to be the main regulator of glomerular perfusion rate and pressure, is a notable example. Persons with diabetes who have a tendency for microangiopathy appear to exhibit a progressive inability to convert inactive renin precursor to active renin.[16] Notwithstanding a similar tendency towards hypoangiotensinemia, diabetic rats fail to upregulate glomerular receptors to angiotensin II.[17] Thus, the constrictor influence of this important hormone on the glomerular microcirculation appears to be blunted in the diabetic state. The imbalance in favor of vasodilatation may be compounded by excessive production of prostaglandins E_2 and I. In vitro production of these vasodilator cicosanoids by glomeruli or mesangial cells isolated from diabetic rats has been shown to be enhanced.[18,19]

The postulate that diabetic glomerular injury is hemodynamically mediated has proved very attractive to clinicians, not least because it holds promise of a therapeutic strategy that might prevent the development of sclerosing glomerulopathy. Irrespective of the precise abnormality of vasoregulation that leads to the glomerular overperfusion, the aforementioned observations in rats suggest that any measure that lowers the glomerular perfusion rate and pressure will protect the animal in a nonspecific fashion from the ravages of diabetic glomerulopathy. However, several unresolved issues merit careful consideration before this hypothesis is extrapolated to humans. Still to be determined, for example, is whether streptozocin-induced diabetic glomerulopathy in rats is indeed a precise analogue of the human disease. Whereas mesangial expansion has been described in persons with diabetes to be generalized and global (hence the term diffuse intercapillary diabetic glomerulosclerosis), the corresponding glomerular lesion in rats is focal and segmental.[13,14,20] Also, the large acellular mesangial nodules, described half a century ago by Kimmelstiel and Wilson and thought to be pathognomonic of human diabetic glomerulosclerosis, do not occur in rodents. Furthermore, there is to date no study that has shown renal plasma flow to be elevated in persons with diabetes of recent onset, notwithstanding coexistent hyperfiltration.[8,9,21] Given the consistent finding of glomerular enlargement in early diabetes, it is conceivable that an increase in surface area for filtration results in an enhanced ultrafiltration capacity of glomerular capillaries and that this phenomenon, rather than an elevated glomerular ultrafiltration pressure, is the proximate determinant of hyperfiltration.[1]

It is also worthy of emphasis that unlike the clearly delineated course from early hyperfiltration to sclerosing glomerulopathy in diabetic rats, this linkage in humans is, at best, tenuous. To date, two groups of workers have reexamined patients with type I diabetes 8 to 16 years after hyperfiltration or microalbuminuria or both were first documented.[22,23] Their findings suggest that those who at reexamination exhibited proteinuric glomerulopathy were the subjects with the highest levels of microalbuminuria (and perhaps hyperfiltration) at the time of initial examination. It is important to realize, however, that the total population subjected to such sequential examination numbers only 107 and, of these, proteinuric glomerulopathy developed in fact in only 21. Clearly, before every person with newly diagnosed diabetes mellitus is subjected to decades of therapy designed to lower glomerular pressures and flows, whether by dietary or pharmacologic manipulation or by continuous subcutaneous insulin infusion, it is necessary that the pathogenetic sequence from early hyperfiltration and microalbuminuria to sclerosing glomerulopathy in humans be more convincingly documented.

In our quest to understand better the pathogenesis of the diabetic glomerulopathy, it is important that we not indulge in oversimplification by ascribing entirely the glomerular injury to elevated glomerular pressures and flows. There are a number of compositional changes that distinguish the glomerular basement membrane in diabetic persons from normal. Either glycosylation of its structural proteins[24] or a reduction of the negatively charged, sulfated proteoglycans that normally reside in the basement membrane[25] could alter its permeability properties, thereby accounting for microalbuminuria. Such metabolic and/or structural alteration of the intrinsic properties of the diabetic glomerular capillary wall need not, of course, be an exclusive explanation for the subsequent development of diabetic glomerulopathy. Indeed, coexistent glomerular capillary overperfusion and hypertension could be unusually noxious to a capillary wall whose composition had been altered by the diabetic state. Clearly, a great deal of investigation remains to be done before the pathogenesis of diabetic glomerulopathy is elucidated. In the meantime, circumspection needs to be exercised by the clinical community before, based on the hemodynamic theory of the genesis of diabetic glomerulopathy, it embarks on extraordinary therapeutic efforts in diabetic patients aimed at lowering the glomerular filtration rate. Such therapy must, of necessity, be administered over many years and may prove in the final analysis to be futile.

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Of Physicianship and Patienthood

In a recent issue of the journal *Daedalus*, Eric Cassell makes a number of insightful points.[1] He is discussing the changing concept of the ideal physician and the changing character of physicianship and patienthood. He notes that medicine's embrace of science has been almost total, that physicians have been seduced (my term) by the "disarming simplicity and certainty of technology" and that over time, power in the medical establishment has shifted from clinician to scientist—that is, the physician role model is now more the medical scientist rather than the clinician. While more or less at the same time, the words "person" and "individual" have taken on new meaning as the public has become more aware and self-assertive. Cassell contends that all of this has had profound effects on physicianship and patienthood, and indeed he may be right.

None of the above is likely to change, at least right away. But there are flaws in some of what is going on. There is much more to physicianship than a mastery of science and technology, and there is much more to patienthood than personal awareness and self-assertiveness. Certain things are important to remember. For one, all science is value free. It is amoral. It deals primarily with general laws. It is impersonal. Medicine, on the other hand, has a long tradition of values, and it deals with persons as individuals whose personal needs and ailments are not often described or measured in scientific terms. While medicine and science have become inextricably bound, as Cassell says, they are not and cannot be one and the same. The assumption by some younger physicians (and even some medical educators), and much of the public, that medicine is now all science, is simply not valid. And as for those who espouse the modern view of patienthood, they often seem to forget that patients come to physicians or to the medical establishment seeking help. They seek something they cannot supply themselves, to relieve or cope with their real or perceived pain, fear, discomfort, anxiety or whatever. These needs are individual, personal and value laden. Physicianship that depends only on impersonal and value free science and technology will not and cannot fill this need. Nor will patienthood that relies entirely on awareness and self-assertiveness succeed in filling this need for something beyond that which a patient can supply on his or her own.

Today physicianship and patienthood are both on trial. Physicians are jumpy, living with inadequacies inherent in their science, third party pressures on what they do or do not do, and with the current conventional wisdom that patient care is some sort of impersonal commodity to be bartered at the cheapest price in the marketplace. Patients are trying to make their own health care decisions as much as they can, and looking for someone to blame if there is any failure. And, too often, the doctor-patient relationship may be virtually nonexistent or, if present, may be more adversarial than truly collaborative.

But there are some countervailing trends. There is a new emphasis on primary care in training programs for general internal medicine, pediatrics and particularly in the family practice movement. In these and some other programs the art is being taught as well as the science. In the practice arena there is a recent and now perceptible interest in better payment for the cognitive services of physicians in whatever specialty, services that are so essential for meaningful physicianship and patienthood. And then there is a growing academic, practitioner and public interest in many of the personal, human, ethical and judgmental aspects of patient care. It is even possible that if and when the art and science become better balanced in patient care, there might just be some favorable effect on the cost. But all this will take some time.

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Case Reports

Recurrent Meningoencephalitis With Recovery From Behçet's Disease

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RECURRENT MENINGOENCEPHALITIS in a patient whose cerebrospinal fluid cultures are sterile is uncommon but can occur with the Vogt-Koyanagi-Harada syndrome, Mollaret's meningitis, granulomatous angiitis, sarcoidosis and following leaks of dermoid or epidermoid cysts. Acute meningoencephalitis is a recognized complication of Behçet's disease, but patients in the past have generally had single attacks or episodes associated with permanent neurological sequelae.[1-3] We report the first brain biopsy in a man with distinct episodes of meningoencephalitis from Behçet's disease.

Report of a Case

The patient, a 39-year-old Palestinian man, a petroleum engineer, first noted recurrent aphthous ulcers on lips and perirectal areas five years earlier. He also experienced episodes of right iritis, erythema nodosum and severe migratory arthralgias. Four years earlier, one- to two-day episodes of unexplained fever of 39.4°C (103°F) developed that were associated with delirium. Two years earlier he had a 40.5°C (105°F) fever, arthralgias and delirium. Over the next 24 hours he lapsed into a semicoma. On general physical examination, no abnormalities were found and neurologic examination showed no focal abnormalities. A specimen of the cerebrospinal fluid (CSF) had 325 lymphocytes per μl, 121 mg per dl protein, 67 mg per dl glucose and sterile bacterial, tuberculous and fungal cultures. A computed tomographic (CT) scan of the head was normal. The electroencephalogram (EEG) showed excessive background slowing. The patient made a full recovery and returned to work.

The day before admission, acute delirium developed and the patient had a temperature of 40°C (104°F). On admission he was confused and agitated. There was an old quiescent right iritis. General physical and neurological examinations otherwise showed no abnormalities. Over the next two days, the patient became comatose and responsive only to deep pain. He required endotracheal intubation and mechanical ventilation. A right hyperreflexia with a right Babinski sign was now present. The leukocyte count was 16,100 per μl without eosinophils. Serum electrolyte values and liver and renal function studies were normal. The CSF had 280 leukocytes per μl (75% neutrophils), 25 erythrocytes per μl, 51 mg per dl glucose, 96 mg per dl protein and sterile bacterial, fungal and viral cultures. The EEG showed diffuse slowing greatest on the left side. Noncontrasted and contrasted CT scans of the head were normal.

Early during the hospital stay, the patient's past history was incomplete. Therefore, a right frontal brain biopsy was done to rule out herpes simplex encephalitis. The patient was treated with methylprednisolone sodium succinate, 1 gram per day for five days. He made a full recovery over that week.

Brain Biopsy Findings

By light and electron microscopy, numerous perivascular infiltrates consisting of lymphocytes, large mononuclear cells and occasional hemosiderin- and lipid-laden macrophages were seen throughout the 1 by 0.5-cm piece of frontal cortex (Figure 1). These cells were limited to the Virchow-Robin spaces. In several small vessels, the endothelial lining was missing and the wall was replaced by fibrinlike material. In the subcortical white matter, the changes were milder. Rare microglia were found near blood vessels. No demyelination or inclusion bodies were seen. A mild lymphocytic infiltrate of the meninges was present. Giemsa and Levaditi stains showed no microorganisms and none were seen by electron microscopy. Bacterial and fungal cultures of the biopsy were sterile. Homogenates (10%) of the biopsy specimen were inoculated into HeLa, low-passage human foreskin fibroblasts, rhabdomyosarcoma, baby hamster kidney (BHK-21) and buffalo green monkey cells. In addition, brain explants were cocultivated with low-passage human foreskin and BHK-21 cells for three weeks. No viruses were isolated.

Comment

The diagnosis of Behçet's syndrome was based on recurrent oral and perirectal ulcers, anterior uveitis, erythema nodosum, fevers with arthralgias, episodes of neurological dysfunction and findings on brain biopsy consistent with the diagnosis.[4] Behçet's disease has central nervous system (CNS) manifestations in 4% to 42% of patients.[5] In two thirds the onset of neurologic disease is sudden and in one third gradual.[1] The brain biopsy confirms what has been previously reported from scattered autopsies. These findings include a lymphocytic meningitis, vasculitis, perivascular cuffing of parenchymal blood vessels and thrombosis of arterioles, venules, veins and dural venous sinuses.[1,6-10] Focal necrotic areas, not seen in our material, are often scattered throughout the brain but have a predilection for the basal ganglia and brain stem.[1,6,8,10] The absence of necrosis in the brain of our patient could represent a sampling error or suggest milder disease that allowed for clinical recovery.

The clinical features of Behçet's disease fall into three broad categories with some overlap: (1) diffuse CNS involve-

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ABBREVIATIONS USED IN TEXT

CNS = central nervous system
CSF = cerebrospinal fluid
CT = computed tomography
EEG = electroencephalogram

ment with acute meningoencephalitis, organic psychosis or progressive dementia; (2) predominantly brain-stem or spinal cord involvement with cranial nerve palsies, hemiparesis, paraparesis, ataxia, pseudobulbar palsy or parkinsonism, and (3) thrombosis of major intracranial draining veins causing intracranial hypertension with headaches and papilledema. Once CNS involvement is present, a relapsing and fluctuating course develops in about half the patients, with permanent neurologic sequelae. Fortunately, some patients improve remarkably, as did our patient who recovered from several bouts of delirium and two episodes of coma.

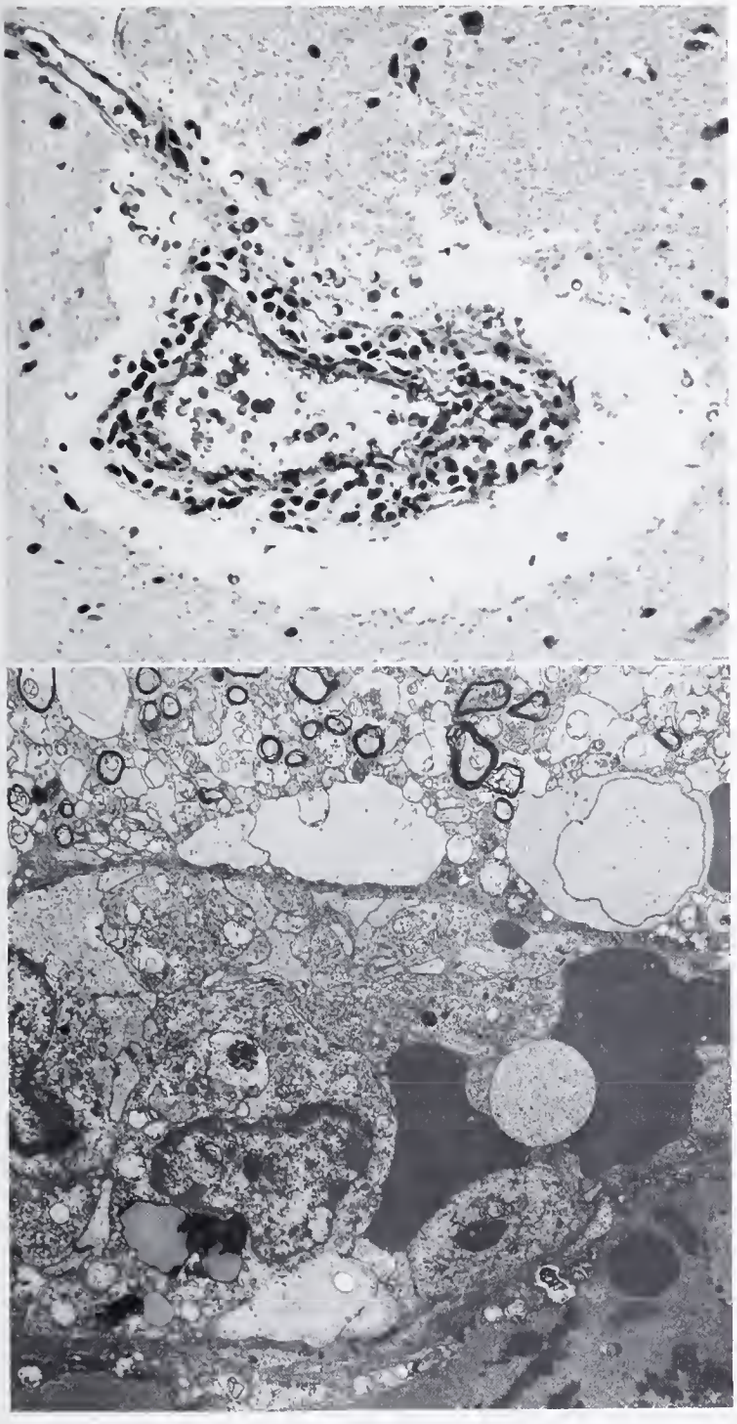

Figure 1.—Photomicrographs of right frontal cortex. **Top**, The perivascular space contains numerous large and small mononuclear cells; its outer limit is separated by artifact from surrounding parenchyma, which is histologically normal (hematoxylin and eosin, × 190). **Bottom**, Electron micrograph shows aggregated macrophages distending the perivascular space of a small blood vessel cut longitudinally. A few extravasated erythrocytes are admixed (× 11,900).

Behçet's syndrome should be included in the differential diagnosis of unexplained recurrent meningoencephalitis. A history of recurrent aphthous ulcers of the lips and genital areas, iritis and other signs of Behçet's disease should be sought. Although the disease is most common in Middle Eastern and Japanese men, Behcet's disease does occur in the United States.

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Münchausen's Syndrome Presenting With Postphlebitic Syndrome

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MÜNCHAUSEN'S SYNDROME is feigned illness presented in a plausible manner to gain hospital admission. The illness is listed as a chronic factitious disorder with physical symptoms in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*.[1] The syndrome takes its name from Baron Karl Friedrich Hieronymus von Münchhausen.[2] The 18th-century German baron was known to entertain friends with greatly exaggerated stories. Asher, in 1951, first used the name Münchausen to describe three patients with dramatic gastrointestinal complaints that could not be correlated with surgical or pathologic findings.[3] In recent years, the syndrome has described hospital abusers with con-

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cealed histories of extensive travel and hospital admissions. Patients frequently have self-inflicted signs and symptoms, undergo elaborate medical and surgical investigations and leave hospitals against medical advice.[4]

Patients have targeted all organ systems for their fictional symptoms. In the following report, we describe a patient with the postphlebitic syndrome posing as a case of recurrent acute deep vein thrombophlebitis.

Report of a Case

The patient, a 46-year-old morbidly obese man, presented in February 1984 to the Phoenix Baptist Hospital emergency room with a five-day history of bilateral leg pain and paresthesias and swelling of his left calf.

The patient's home was in Montana, but he was itinerant and had no local physician. He reported having recurrent thrombophlebitis, possibly 30 episodes, and several episodes of pulmonary embolus. His original injury was reported as a gunshot wound to his left lower leg in 1979. He was then employed as an industrial security guard and all related medical care was covered by Workers' Compensation. His first episode of thrombophlebitis followed soon after. An inferior vena caval umbrella was placed in 1981, following his second pulmonary embolus, confirmed by findings of a lung scan. He reported three more episodes of pulmonary embolus after that operation, however. His last episode of thrombophlebitis occurred two months earlier, at a hospital in Albuquerque he could not remember. The patient reported a "bad venogram" was done at that time and he was admitted to hospital for two weeks of intravenous heparin therapy.

The patient said he had not had trauma, long car rides or other prolonged periods of leg inactivity during the previous two weeks. He stated that his current symptoms exactly mimicked his previous episodes of thrombophlebitis. His physician in Montana, he said, recommended hospital admission for intravenous heparin therapy whenever he experienced these symptoms.

The patient said that resistance to warfarin sodium (Coumadin) developed. He reported being studied at the University of Washington Hematology Section in Seattle. They recommended a daily warfarin dose of 50 mg. The patient had several bleeding episodes on that dosage, however, and lowered it himself.

He reported compliance with his only current medication of 20 mg of warfarin daily. His family history was positive for exogenous obesity in both parents and all siblings. The patient had smoked one pack of cigarettes a day for the past seven years and occasionally used alcohol.

On physical examination he weighed 133 kg (294 lb) and complained of left leg discomfort. The patient was afebrile and other vital signs were normal. His chest was clear bilaterally and heart sounds were muffled by his large chest. The abdomen was soft and nontender. The left lower leg was the most tender, but mild tenderness was noted on palpation of the entire lower extremities. Minimal erythema was observed in the lower part of the left leg. Lower leg circumferences for both legs were equal when measured 5 cm below the tibial tubercles. The patient grimaced on Homan's testing of the left leg. Moderate edema was present at the ankles bilaterally, improving with elevation. There was hyperpigmentation of the skin, decreased hair growth and mild atrophy of the skin over the medial lower legs. No ulcerations or scarring were present.

Studies done on admission showed normal thyroid function, chest film and electrocardiogram, and results of chemistry tests and urinalysis were normal. The leukocyte count was 13,300 per μl with a normal differential. The triglyceride level was elevated to 435 mg per dl. Prothrombin time was 14.7 seconds with a control of 11.6 seconds. The partial thromboplastin time was normal.

The patient was admitted to hospital to rule out recurrent thrombophlebitis. He was given a 10,000-unit bolus of heparin intravenously, followed by 1,500 units an hour by continuous intravenous drip. His left leg was elevated and heat applied. The next morning, a vascular surgeon was consulted. The diagnosis of postphlebitic syndrome was confirmed from the constellation of chronic phlebitis changes evident in the legs. A venogram was not done since it was believed that one was abnormal in the recent past.

Several phone calls were made to obtain further history. The patient's physician in Montana had lost contact with him two years earlier. The patient was granted full compensation for medical coverage by the Montana Division of Workers' Compensation after being hit by a gate in 1980. His recurrent problems with thrombophlebitis and possible pulmonary emboli led to many hospital admissions in several western states (Table 1). Those who evaluated him at the Hematology Section at Virginia Mason Hospital in Seattle felt he had warfarin resistance. Subsequent bleeding episodes led his physicians to believe that he had increased warfarin requirements due to his massive body size.

On the third hospital day, the patient was receiving 2,000 units of heparin per hour, as well as 20 mg of warfarin daily. The partial thromboplastin time was 66.4 seconds with a control of 30.7 seconds. The prothrombin time was 18.0 seconds with a control of 11.9 seconds. The patient's symptoms persisted and he became very demanding of nursing personnel. He became vague in his historical data as he was confronted with previously concealed information. Rapid resolution of his symptoms was noted on the fourth day.

The diagnosis of Münchausen's syndrome had been entertained during several previous hospital admissions. Psychiatric consultation, obtained during this admission, confirmed the diagnosis of a fictional disorder consistent with Münchausen's syndrome.

The patient was discharged on the fifth hospital day for outpatient follow-up. The daily warfarin dose was continued at 20 mg. The patient refused to wear support stockings or to quit smoking, as recommended. He did not keep his follow-up outpatient appointments.

Discussion

The postphlebitic syndrome is a recognized complication of deep vein thrombosis. The syndrome is estimated to exist in 1% to 2% of the general population.[5] In accordance with the incidence of deep vein thrombosis, the syndrome is more common in the left leg.

The loss of valvular competence in the deep venous system produces ambulatory venous hypertension and corresponding skin changes.[6] Ulceration has been reported in as many as 20% of patients within five years of the onset of the disease. Stasis pigmentation, alopecia and edema were all seen in this

patient. Pain has also been frequently recognized as a component of this syndrome.[6] The rapid disappearance of this patient's pain after he was confronted with the concealed medical history made his account of pain suspect.

The clinical diagnosis of deep vein thrombosis is notoriously inaccurate.[7] The disease is frequently present in the absence of symptoms, as well as being absent in half of patients in whom clinical signs or symptoms suggest its presence. The radiologic standard for identifying deep vein thrombosis is the venogram. The age of the thrombotic changes is not always apparent from the venogram,[8] so the test may not be able to distinguish new from old disease. With the postphlebitic syndrome, the deep venous system may show residual abnormalities. Chronic disease frequently causes the contrast medium to flow preferentially through the superficial system.[8]

Chronic venous change may also make it technically difficult to inject contrast medium into the leg for a venogram. Two noninvasive procedures used in detecting disease include impedance plethysmography and Doppler flow studies. Radiofibrinogen leg scanning is also used, but this test also requires injection. While these tests all have their limitations, they can greatly aid in diagnosis when selectively done together or in combination with the venogram.[7] Several newer tests may be helpful in diagnosing chronic disease and the postphlebitic syndrome. Descending (rather than ascending) venography has shown efficacy in diagnosing chronic venous damage.[9] Elevated Doppler venous pressures have been noted with the postphlebitic syndrome.[10]

TABLE 1.—*List of Hospital Admissions**

October 1980	Deaconess Hospital	Billings, Mont
November 1980	St Vincent's Hospital	Billings, Mont
November 1980	Deaconess Hospital	Billings, Mont
December 1980	St Vincent's Hospital	Billings, Mont
December 1980	Central Montana Hospital	Lewistown, Mont
February 1981	St Patrick's Hospital	Missoula, Mont
March 1981	Deaconess Hospital	Great Falls, Mont
March 1981	St Patrick's Hospital	Missoula, Mont
April 1981	Kalispell Regional Hospital	Kalispell, Mont
July 1981	St James' Hospital	Butte, Mont
September 1981	Penrose Hospital	Colorado Springs, Colo
September 1981	Memorial Hospital	Colorado Springs, Colo
October 1981	McKee Medical Center	Loveland, Colo
October 1981	Sheridan County Memorial Hospital	Sheridan, Wyo
November 1981	St James' Hospital	Butte, Mont
November 1981	Virginia Mason Hospital	Seattle
December 1981	St James' Hospital	Butte, Mont
January 1982	Desert Springs Hospital	Las Vegas
March 1982	Virginia Mason Hospital	Seattle
April 1982	St Peter's Hospital	Helena, Mont
July 1982	St Patrick's Hospital	Missoula, Mont
October 1982	St Patrick's Hospital	Missoula, Mont
November 1982	Coulee General Hospital	Grand Coulee, Wash
June 1983	St Peter's Hospital	Helena, Mont
July 1983	St Peter's Hospital	Helena, Mont
October 1983	St Peter's Hospital	Helena, Mont
November 1983	St Peter's Hospital	Helena, Mont
November 1983	Desert Springs Hospital	Las Vegas
December 1983	Desert Springs Hospital	Las Vegas
December 1983	Heights General Hospital	Albuquerque
January 1984	Scottsdale Memorial Hospital	Scottsdale, Ariz
January 1984	St Luke's Hospital	Phoenix
February 1984	Phoenix Baptist Hospital	Phoenix
February 1984	Phoenix General Hospital	Phoenix
March 1984	Desert Springs Hospital	Las Vegas
April 1984	Southern Nevada Memorial Hospital	Las Vegas
May 1984	Desert Springs Hospital	Las Vegas
September 1984	Seward General Hospital	Seward, Alaska

*Compiled in December 1984.

Patients presenting with possible thrombophlebitis generally should undergo diagnostic confirmation before instituting heparin therapy.[7] This patient presented in the evening and heparin therapy was begun before study, until his suspicious history and findings could be scrutinized. The morning following admission, it was learned that numerous studies during several previous hospital admissions revealed chronic disease. A venogram done just several weeks before this admission, in New Mexico, showed only chronic changes.

Patients with Münchausen's syndrome frequently submit to excessive medical testing. Repeated diagnostic testing and medical attention may support the unusual behaviors exhibited by Münchausen's patients. In light of the recently confirmed chronic disease and good support for the diagnosis of Münchausen's syndrome, our consultants suggested minimal further diagnostic workup.

Many of the salient features of chronic factitious illness were evidenced in this patient. His illness began with a legitimate physical problem. The patient had a concealed history of many hospital admissions with extensive travel. His medical history had a dramatic flair initially; however, the patient became vaguer and more inconsistent on further questioning. He became very demanding of medical personnel. While the patient did not leave against medical advice, as is common for patients with Münchausen's syndrome, the treatment recommendations were not followed.

The list of this patient's hospital admissions is impressive (Table 1). We were not aware of his many hospital admissions in Phoenix until well after discharge. He visited several hospitals in the same city on different occasions, and he was known to leave against medical advice at least once in 1981.

The charges for hospital admissions and professional fees for Münchausen's patients frequently are not recovered, and the costs are absorbed. This case represented an estimated expense to the state of nearly $100,000. We reported our findings to the Montana Division of Workers' Compensation and recommended reevaluation of this patient's current status.

The diagnosis of Münchausen's syndrome is not easily made in the emergency department or on initial presentation. A suspicion of fictional illness, when coupled with an unusual or inconsistent history and the postphlebitic syndrome, may aid an admitting physician to avoid unnecessary procedures or hospital admission.

The postphlebitic syndrome is not listed as a common manifestation of Münchausen's syndrome.[1,4] We hope this report will encourage physicians to consider this disorder's potential for being used fictitiously.

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Severe Pulmonary Hypertension in a Patient With Rheumatoid Arthritis—Response to Nifedipine

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SEVERE PULMONARY HYPERTENSION in patients with rheumatoid arthritis is rare[1] and is more commonly associated with other collagen-vascular diseases such as progressive systemic sclerosis[1,2] or the syndrome of calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly and telangiectasia.[3] Precapillary pulmonary hypertension in patients with rheumatoid arthritis may be found when the condition is complicated by pulmonary fibrosis.[4] Severe pulmonary hypertension associated with rheumatoid arthritis in those patients with no clinical evidence of pulmonary parenchymal involvement is thought to be caused by pulmonary arteriolar vasospasm or pulmonary vasculitis.[5] This latter group of patients with no apparent parenchymal involvement appears clinically similar to patients with primary pulmonary hypertension except for the arthritis.[1,5,6]

Recent reports of the efficacy of vasodilator therapy in patients with primary pulmonary hypertension[7-10] prompted us to evaluate the calcium channel blocker nifedipine in a patient with rheumatoid arthritis, Raynaud's phenomenon and severe precapillary pulmonary hypertension.

Report of a Case

The patient, a 61-year-old man with a 30-year history of rheumatoid arthritis, presented with dyspnea, episodes of near syncope and Raynaud's phenomenon. He had a 30-pack-year smoking history and had worked in a foundry. For the two years before presentation he was treated with gold and naproxen.

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On physical examination he had normal breath sounds, a right ventricular heave, an increased pulmonic second sound, subcutaneous nodules and joint changes consistent with rheumatoid arthritis. The rheumatoid factor was 1:5,120 and an antinuclear antibody test was negative. An electrocardiogram (Figure 1) showed right atrial enlargement and right ventricular hypertrophy. A chest roentgenogram (Figure 2) showed enlarged main pulmonary arteries and cardiac silhouette. The lung fields were normal.

Pulmonary function data over a 28-month period are listed in Table 1. These values give no evidence of a significant obstructive or restrictive defect. The single breath test of the diffusing capacity of the lung for carbon monoxide and results of a ventilation-perfusion lung scan were normal. There was no activity over the kidneys to suggest a right to left shunt. A two-dimensional echocardiogram showed an enlarged right atrium and right ventricle with paradoxical motion of the

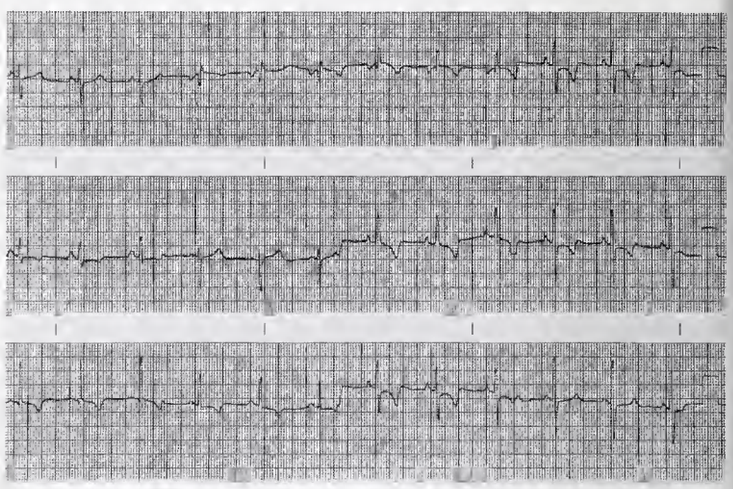

Figure 1.—An electrocardiogram done on a 61-year-old patient shows right atrial enlargement and right ventricular hypertrophy.

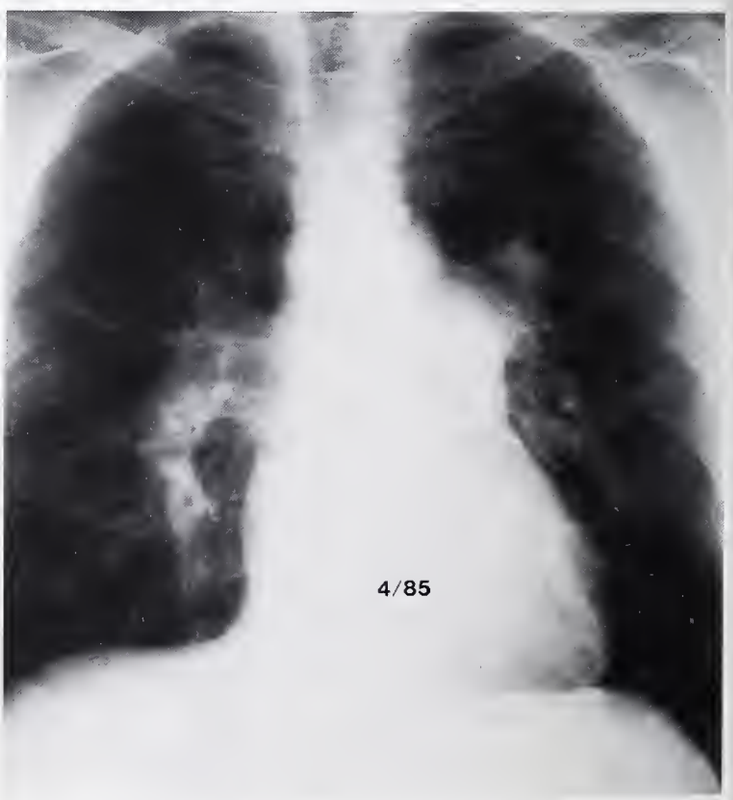

Figure 2.—A chest roentgenogram shows enlarged main pulmonary arteries and cardiac silhouette.

ABBREVIATIONS USED IN TEXT

Pa_{O_2} = partial pressure of arterial oxygen
PAP = pulmonary artery pressure
Sa_{O_2} = arterial saturation of oxygen

TABLE 1.—*Pulmonary Function Data*

Pulmonary Function Tests	December 1982*	June 1984*	April 1985*
FVC, liters	3.79 (82%)	3.73 (84%)	3.35 (76%)
FEV 1, liters	2.83 (86%)	2.80 (89%)	2.48 (80%)
FEV 1/FVC, %	74	75	74
DLCO, (ml/min/mm Hg)	17.2 (79%)	19.2 (91%)	19.2 (93%)

DLCO = diffusing capacity of the lung for carbon monoxide, FEV 1 = forced expiratory volume in 1 second, FVC = forced vital capacity

*Numbers in parentheses represent percent of predicted.

septum. The left ventricle and left atrium were normal. No right to left shunt was noted after an agitated saline contrast injection. A gallium 67 scan showed uptake over the carpal and metacarpophalangeal joints of both hands but no pulmonary uptake. A skin biopsy specimen taken from the lower extremity was interpreted as showing leukocytoclastic vasculitis.

The results of pulmonary artery catheterization and arterial blood gas determinations are listed in Table 2. Baseline hemodynamics showed severe precapillary pulmonary hypertension (mean pulmonary arterial pressure [PAP] of 78 mm of mercury) with no response to hyperoxia (partial pressure of arterial oxygen [Pa_{O_2}] 202 mm of mercury, mean PAP 77 mm of mercury). Thirty minutes after the oral administration of 10 mg of nifedipine, the mean PAP decreased to 63 mm of mercury and the pulmonary vascular resistance decreased from 1,547 dynes·sec·cm^{-5} to 877 dynes·sec·cm^{-5}. Repeat pulmonary artery catheterization eight months after the patient had been treated with nifedipine, 10 mg orally every eight hours, showed a sustained reduction in the mean PAP (52 mm of mercury) and the pulmonary vascular resistance (901 dynes·sec·cm^{-5}). In addition, the patient noted a substantial improvement in his exercise tolerance and no occurrence of Raynaud's phenomenon. Before nifedipine therapy, he could not walk one block without having severe dyspnea. While on nifedipine therapy, he was able to climb two flights of stairs with only minimal dyspnea. The resting Pa_{O_2} decreased from 72 mm of mercury to 60 mm of mercury, however.

Discussion

The association of primary pulmonary hypertension with a vasoconstrictive disorder such as Raynaud's phenomenon suggests that the pulmonary hypertension may be due to pulmonary vasoconstriction in response to an unknown stimulus.[5,11] An early histologic lesion in many patients with primary pulmonary hypertension is medial hypertrophy of pulmonary arterioles.[5] Similar histologic findings have been described in patients with rheumatoid arthritis and severe pulmonary hypertension.[5,12] We believe that our patient's condition fits into the category of primary pulmonary hypertension associated with rheumatoid arthritis. The normal spirometry and diffusing capacity, absence of parenchymal densities on the chest roentgenogram and absence of pulmonary uptake of ^{67}Ga reasonably excludes rheumatoid arthritis-associated pulmonary fibrosis that could lead to pulmonary hypertension.

Our patient had significant hemodynamic improvement and symptomatic relief of his dyspnea while receiving nifedipine. While we ascribe the hemodynamic improvement to the administration of the drug, we admit the possibility that the hemodynamic changes may have been spontaneous. In patients with primary pulmonary hypertension, the PAP may be labile, with wide fluctuations in the mean PAP (70 to 40 mm of mercury) having been reported.[13]

We, along with others,[14] recommend caution in administering vasodilators to patients with severe pulmonary hypertension. Several untoward effects, including systemic hypotension, worsening pulmonary hypertension, systemic arterial oxygen desaturation (Sa_{O_2}) and even sudden death have occurred after vasodilator administration in patients with primary pulmonary hypertension and other severe pulmonary hypertensive states.[14,15] Systemic arterial oxygen desaturation may be of especial concern in patients with a borderline Pa_{O_2} near 60 mm of mercury, because a further reduction in the Pa_{O_2} will lead to a dangerously low Sa_{O_2}. A

TABLE 2.—*Hemodynamics and Arterial Blood Gas Values*

	August 1984			April 1985
	Baseline Values	With Oxygen*	With Nifedipine	Nifedipine
Heart rate, bpm	77	74	79	70
Systemic BP, mm Hg	125/70	140/80	115/65	120/80
PAP, mm Hg	125/50	120/55	90/35	75/40
PAP, mean	78	77	63	52
PCWP, mm Hg	12	12	10	11
Cardiac output, liters/min	3.31	3.23	4.64	3.64
SVR, dynes·sec·cm^{-5}	1,837	2,180	1,207	1,802
PVR, dynes·sec·cm^{-5}	1,547	1,628	877	901
pH	7.42	7.44	7.43	7.43
Pa_{CO_2}, mm Hg	29	23	25	33
Pa_{O_2}, mm Hg	72	202	69	60

BP = blood pressure, Pa_{CO_2} = partial arterial pressure of carbon dioxide, Pa_{O_2} = partial arterial pressure of oxygen, PAP = pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure, PVR = pulmonary vascular resistance, SVR = systemic vascular resistance

*High-flow, tight-fitting, nonrebreathing mask with reservoir bag was used.

low Sao_2 combined with a reduced cardiac output will severely compromise oxygen delivery to the periphery. Vasodilator trials in these patients, therefore, should be done under hemodynamic monitoring with attention to the effects on the Sao_2. Our patient had worsening gas exchange as evidenced by a fall in the Pao_2 from 72 mm of mercury to 60 mm of mercury, possibly resulting from worsening ventilation-perfusion relationships caused by nifedipine.[16,17]

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Earwig in the Ear

TO THE EDITOR: Earwigs are nocturnal, drab-colored insects of the order *Dermaptera* that are attracted to light and occasionally creep into homes. Their chewing mouthparts and forceps-like abdominal appendages give them a foreboding appearance.

The common name for these anthropods in at least six European languages incorporates a word for ear. The extended hindwing of some species resembles the shape of a human ear and the earwig's pincers look like instruments once used to pierce women's ears for earrings. Furthermore, there is an ancient Anglo-Saxon legend that they crawl into the ears of sleeping persons. Entomologists, however, insist that this belief is without foundation.[1-3] The following is the second report from Arizona—and also only the second in English literature—to document the veracity of the legend.

At 3 AM, my 8-year-old daughter awoke me from a sound sleep. She was extremely upset. For the preceding few minutes she had attempted to remove a creature crawling about in her left external ear canal. A light sleeper, she had been aroused by "the sound of little feet." Otoscopic examination revealed a dark brown mass near the tympanic membrane. My brief discussion with her on the importance of proper hygiene was interrupted when I saw the form move. Then, bathed in brilliant illumination from the otoscope, a female earwig (family, *Carcinophoridae*), measuring 20 mm in length, cautiously emerged, to the relief of insect, child and father.

Earwigs do not, as once believed, enter the brain to cause insanity but they can enter the external ear canal while we sleep. Some species pinch sharply and forcibly eject a highly irritating fluid from abdominal glands.[4] In the previous report[5] a male European earwig (*Forficula auricularia*) punctured and lacerated the tympanic membrane of a sleeping graduate student in Flagstaff, Arizona.

Earwigs are relatively harmless and, in all likelihood, enter the human ear rarely and only by chance. Nevertheless, they can produce severe otic trauma lending credence to an ancient "myth."

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Costs and Value of Screening Flexible Sigmoidoscopy

TO THE EDITOR: The article by Rumans and associates[1] in the June 1986 issue, which justifies the cost-effectiveness of screening flexible sigmoidoscopy in asymptomatic patients over 50 years of age with three stool tests (Hemoccult) negative for occult blood, will be helpful for my marketing program. The following questions, however, remain unanswered:

- Of the malignant lesions and precancerous polyps discovered, how many would eventually have been detected by Hemoccult tests alone or become symptomatic while still curable (if curable can be defined) had no sigmoidoscopy been done?
- What is the value of the lives saved, morbidity avoided and medical care costs unspent as a result of the treatment following these discoveries?
- How do these savings compare to the total program cost per discovered and treated and cured condition, which condition statistically would not have been cured but for the flexible sigmoidoscopy?
- If it is my patient and he or she can pay for the test, how much should cost-effectiveness criteria affect my decision to perform or withhold the examination?

It seems very complicated to prove the cost-effectiveness of this examination.

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EDITOR'S NOTE:

Would that we knew the answers to these questions.

MSMW

Toxicity from BHT Ingestion

TO THE EDITOR: In a letter in the August 1983 issue of the journal, Dr J.G. Llaurado expressed concern over the possible toxicity from ingestion of large amounts of butylated hydroxytoluene (BHT) in the pursuit of a cure for herpes genitalis and of long life.[1] I have just such a case to report.

Report of a Case

A 24-year-old woman, an advertising executive, complained of light-headedness, unsteadiness of gait and slurred speech. The following findings were noted on examination: dysarthria, wide-based gait, a positive Romberg test, slowed mentation without thought disorder and dysmetria of the left (nondominant) arm. The pupils were of normal size and reactivity and there was no nystagmus. Results of routine laboratory studies, including serum electrolyte, bicarbonate, liver and renal function, electrocardiographic and chest x-ray studies, were all normal or within normal limits. Repeat examination eight hours later showed no abnormalities.

The patient said that she had obtained a formula for BHT ingestion as a cure for genital herpes from a man advertising himself in a local newspaper as a "researcher" in herpes treatment. When contacted, the man explained to me that he had read of this treatment in *Secrets of Life Extension* by John A. Mann.[2] On the evening before admission, the patient ingested 80 grams of BHT suspended in safflower oil on an empty stomach. Between 30 and 60 minutes later, she began to experience a light-headed, "high" feeling followed by a severe frontal headache and visual and auditory hallucinations over the next several hours. When she awakened the next morning, she was unsteady on her feet, had slurred speech and complained that sounds and voices were "far away."

Discussion

My review of the medical literature reveals that previously reported human toxicity is confined to suspected allergic reactions.[3] The best source available on human and animal ingestion is the Franklin Research Center review.[4] It reports no evidence of human toxicity in doses as high as 6 grams per day over a course of 30 days. The reported half-life in humans is less than 24 hours, which is consistent with the time course in our patient. Our patient's symptoms and signs and those reported in the literature in animals correlate well.

The source used by Mr Mann in his book to justify BHT to treat herpes is a report by Snipes and associates on the in vitro inactivation of herpes virus by BHT.[5]

Fortunately for our patient, follow-up at six months and one year showed no long-term toxicity. However, she has had outbreaks of her herpes.

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Psychological Factors in Back Pain

TO THE EDITOR: The article on psychological aspects of back pain by Derebery and Tullis in the May issue[1] offers almost a full reprise of the criteria for histrionic personality disorder as stipulated by the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition).

But, having established this diagnosis implicitly, the authors do not make it explicit, nor, indeed, do they account for their not offering any formal *DSM-III* diagnoses among these patently psychiatric patients.

One is nonplussed as to their reasons for this omission.

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* * *

Dr Tullis Responds

TO THE EDITOR: In our experience the majority of the type of patients described in this article do not easily fall into the categories outlined in *DSM-III.* Occasionally, a patient may meet the criteria for one of the disorders such as somatization disorder, conversion disorder, psychogenic pain disorder, hypochondriasis, posttraumatic stress disorder or depression. More often than not, however, the patient is simply manifesting a maladaptive response to stress that does not meet the necessary criteria for one of these diagnoses.

We do not concur that the paper offers a full description of the histrionic personality disorder as outlined in *DSM-III.* Although such patients may manifest some of these traits during the time of their physical problems, it is often not representative of their long-term behavior. The *DSM-III* states very clearly that in the histrionic personality disorder these traits are characteristic of the individual's current and long-term functioning and are not limited to episodes of illness.

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The Layer Cake Phenomenon or Sweet It Isn't

TO THE EDITOR: As pharmacists, we are often asked on clinical rounds about individual drug side effects and adverse effects concerning a patient receiving "polypharmacy." What ensues is a lengthy discourse on sometimes as many as 15 different medications. We have since gone to what we call the "layering method" in describing a drug's beneficial or possible detrimental effects. This method is quite popular with the physicians who have gone into "layering" because it involves listing out and comparing, for each drug, similarity of action, side effects—including possible electrolyte alterations—and how therapy can alter the disease state for better or worse.

All those concerned with patient care should realize that in regard to side effects, a new layer of problems is "layered" upon the patient, or at least potentially so, as each drug is added to the therapeutic regimen. When one is caring for a patient receiving digoxin, parenteral amphotericin B and furosemide, the loss of potassium if not closely monitored can be an extreme misadventure. In our opinion, "layering," which can even be adapted to a computer spreadsheet, is an efficient and simple methodology for examining the clinical pharmacology of patient care. One more word of caution:

When caring for outpatients, it is imperative that a complete clinical history be obtained since a number of different physicians may be "layering" the patient. Even the well-known patient should be asked, "Have you been taking any new drugs since I saw you last." All of us have such "medical nomads" in our practices.

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The Reason for Our Profession

To the Editor: Although we all pretend to be aware of the fact that the reason for the existence of today's vast medical facilities and resources is people, in practice sometimes factors such as our egos, economics, titles, timetables and machines get a higher priority and divert us from that basic and simple fact.

A few months ago I was urgently called to my father's home and discovered that he had had a massive myocardial infarction and was in shock. The paramedics who arrived later began a routine whose urgency and appropriateness was far behind the warranted standards. When I volunteered to take control and also full responsibility, it was taken personally and unkindly, resulting in their lack of cooperation in a variety of ways: purposely delaying morphine administration, parking the ambulance on the other side of the street, stopping at every traffic light in spite of the dying man in the ambulance and numerous other actions that were not to the benefit of the patient and solely represented their ego response. Whether their behavior affected the sad outcome of the night is not clear to me and I have long since attempted to forgive them. Nonetheless, this incident which represented an individual's ego standing in the way of the very basic principle of medical care can serve as a reminder to us that perhaps many times a day such and similar incidents of varying magnitudes are taking place, unfortunately involving health professionals who tend to forget the basic mission in their profession: caring for people.

People are the very reason for the existence of our profession. Without people, there is no need for medical research, medical centers, procedures, equipment, medical schools, nurses, doctors or technicians. In the process of delivering care to people, however, often one of the first casualties is awareness of this basic reason for our profession. Because people come to us for help and because we have spent time learning things they do not know, we sometimes put ourselves at a higher level of intelligence. In high-tech environments we sometimes kneel in front of human-created technology and ignore individual feelings. Our technology at times makes us too disease- and organ-oriented, which leads us to inadvertently ignore the presence of the owner of those organs. Some of us consider it downgrading to spend time with our patients and listen to them and feel for them and truly care for them. With more technological advances the gap between human emotions and the medical profession may even widen to a point that we will act like computers, programmed to perform. In order for all of us to realize the importance of true caring for a patient as a whole, it sometimes helps to put ourselves in the patient's place and to feel the importance of caring and consideration for the individual patient regardless of our academic or professional title.

We each need to start from ourselves and in our practice of medicine constantly remind ourselves that we are here to serve people, not machines, schools or computers. In our medical education we need to put increased emphasis on our basic mission and be certain that the message gets across to all levels of health care professionals. By remembering the very basic reason for our profession, perhaps we can avoid a horrifying machine-dominated, impersonal and compassionless future in medical practice. It should be our aim to securely arm all health care professionals and ourselves with an innate mechanism that incessantly stands in the way of our personal feelings and makes our basic mission a constant number one priority.

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Topics in Primary Care Medicine

Sleep Apnea—Diagnosis and Treatment

ROBERT D. BALLARD, MD, *and* RICHARD J. MARTIN, MD, *Denver*

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

The syndrome of sleep apnea has been described throughout the ages, dating at least to descriptions of Dionysius the Tyrant in the fourth century BC. It is only recently that scientific investigation has led to an understanding of this previously ill-defined syndrome.

Sleep apnea is the currently accepted term for a group of heterogeneous sleep-associated respiratory disorders. The most common of these is obstructive apnea, which is defined as a cessation of airflow during continuous respiratory effort. Obstructive apnea occurs when oropharyngeal pressures become so negative as to exceed the ability of upper airway muscles to maintain patency of the oropharynx. A less common sleep-associated respiratory disorder is central apnea, which is usually defined as the cessation of airflow for at least ten seconds, while no respiratory efforts are made. Patients with central apneas probably suffer from reductions in the chemical control of breathing. Mixed apneas also occur, during which airflow ceases for at least ten seconds, associated with periods of no respiratory effort and respiratory efforts against an occluded upper airway. Finally, primary alveolar hypoventilation (PAH) leads to hypoxia and hypercapnia not associated with apneas. This disorder may be present while awake, but is usually much worse during sleep.

It has become increasingly apparent that a large portion of the adult population, especially the elderly, has mildly abnormal breathing during sleep. This may include simple snoring, a symptom often associated with polysomnographic evidence of partial upper airway obstruction, and brief, recurrent central apneas that may lead to complaints of insomnia. These patterns in their mildest forms do not cause significant hypoxemia, and therefore the need for aggressive therapy is uncertain. As further information regarding the natural history of sleep-associated respiratory disorders becomes available, we may find that such mildly abnormal breathing patterns represent different stages in the development of the sleep apnea syndrome.

These disorders are commonly associated with complaints varying from socially unacceptable snoring to nocturnal insomnia or daytime hypersomnolence. More serious associated conditions may include right and left heart failure, erythrocytosis, cardiac arrhythmias (including sudden death) and even respiratory failure. It is therefore crucial to make the proper diagnosis and the appropriate therapeutic intervention.

Diagnostic Techniques

As in any diagnostic evaluation, a thorough history and physical examination are essential. Tables 1 and 2 list clinical symptoms and features common to patients suffering from sleep-associated respiratory disorders. Recognition of these characteristics should direct a clinician to more definitive testing. The affected patients usually suffer from excessive daytime sleepiness, although they may minimize this symptom. There is frequently some altered sleep behavior, most typically loud snoring, restlessness or insomnia, although enuresis and even somnambulation have been described. Progressive intellectual deterioration and personality changes are often seen. The patient is typically an obese man, although significant disease may occur in slender patients. If a woman, the patient is likely to be postmenopause. On physical examination, as many as 50% of patients may have systemic hypertension, and signs of pulmonary hypertension may be noted in as many as 30% of patients.

Daytime laboratory evaluation may not be helpful in identifying affected patients except that an elevated hemoglobin reflects the erythrocytosis related to nocturnal severe oxygen desaturation. The findings of arterial blood gas determinations and pulmonary function tests usually reflect underlying medical conditions such as chronic obstructive airway disease, obesity, congestive heart failure and neuromuscular disorders.

Flow-volume curves have characteristic shapes in some patients with obstructive apnea. A "saw-tooth" pattern is

(Ballard RD, Martin RJ: Sleep apnea—Diagnosis and treatment. West J Med 1986 Aug; 145:248-250)

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ABBREVIATIONS USED IN TEXT

CPAP = continuous positive airway pressure
PAH = primary alveolar hypoventilation

often observed on the expiratory (and sometimes inspiratory) curve. In addition, flattening of the inspiratory curve with a ratio of forced expiratory flow to forced inspiratory flow, both at 50% of vital capacity, in excess of 1 (consistent with extrathoracic airway obstruction) may be seen. These findings in a patient with clinical features of sleep-associated respiratory disorders substantially increase the likelihood of obstructive apnea.

Various techniques have been used to study the morphology of the upper airway in attempts to predict sleep apnea. These include fiber-optic visualization of the oropharynx, fluoroscopic imaging and computed tomographic scanning of the upper airway, lateral cephalometric roentgenograms and even acoustic reflectance studies of the upper airway. These techniques are of course technically difficult, requiring considerable effort and expertise in their interpretations. Thus they are of little value in a standard medical practice.

Finally, the short-term clinical observation of sleeping patients has recently been evaluated as a screening test. Such bedside observations were found to lack specificity and sensitivity in the diagnosis of sleep-associated respiratory disorders.

It is the current consensus that nocturnal sleep polysomnography is the definitive tool for diagnosing sleep-associated respiratory disorders. Such an evaluation is best done initially in a sleep laboratory, usually in a hospital that is committed to provide high-quality studies. Such studies require a trained technician, a reasonable sleep area and various monitors and recorders, which may be expensive. Such devices are necessary to correctly stage sleep, measure respiratory effort and airflow and continuously monitor oxygenation and cardiac rhythm. Several portable home monitoring systems have recently become available and can provide useful diagnostic information in some cases, at a reduced cost to the patient. These monitors typically record cardiac rhythm, oxygen saturation and respiratory movement and lack the capability for sleep staging, flow monitoring or the exact measurement of respiratory effort. We, therefore, feel the portable monitors are most useful in follow-up studies to evaluate the success of therapy.

TABLE 1.—*Common Clinical Symptoms of Sleep-Associated Respiratory Disorders*

Altered sleep behavior (especially snoring, insomnia, enuresis, sleepwalking)
Daytime hypersomnolence
Failing intellect and personality change
Sexual impotence
Morning headache or nausea or both
Symptoms of heart failure (decreased exercise tolerance, exertional dyspnea)

TABLE 2.—*Common Clinical Features of Sleep-Associated Respiratory Disorders*

Obesity
Hypertension
Male sex
Erythrocytosis
Cardiac arrhythmia (commonly sinus arrhythmia, cyclic tachybradycardia, asystole)
Pulmonary hypertension
Cor pulmonale

Therapy

The goals of treatment in the sleep-associated respiratory disorders are to improve alveolar ventilation during sleep, to control the significant signs and symptoms of disease and to improve overall quality of life. To accomplish this, there are several therapeutic modalities, which we have presented in algorithmic form in Figures 1 and 2.

For convenience, we present therapeutic approaches to obstructive and mixed apneas in Figure 1. One should initially exclude clearly reversible causes of these disorders. For ex-

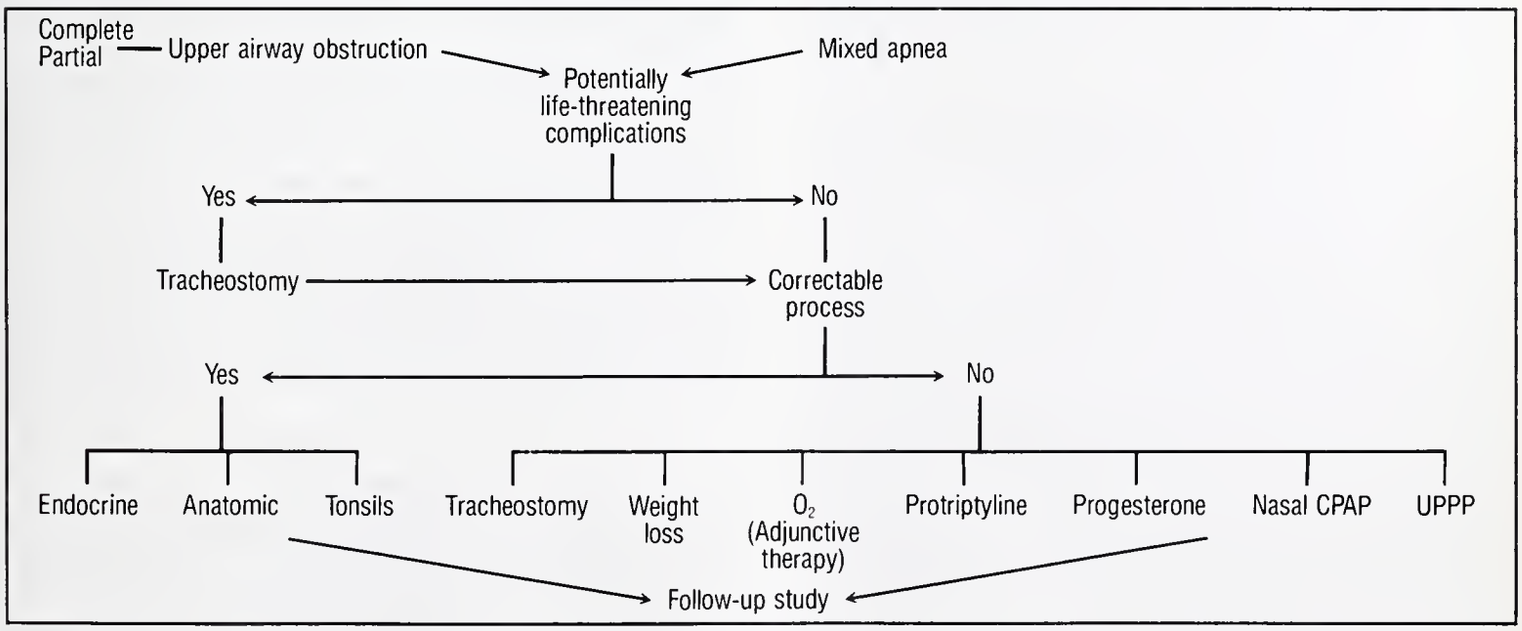

Figure 1.—Algorithm for treating obstructive and mixed apneas. CPAP = continuous positive airway pressure, UPPP = uvulopalatopharyngoplasty

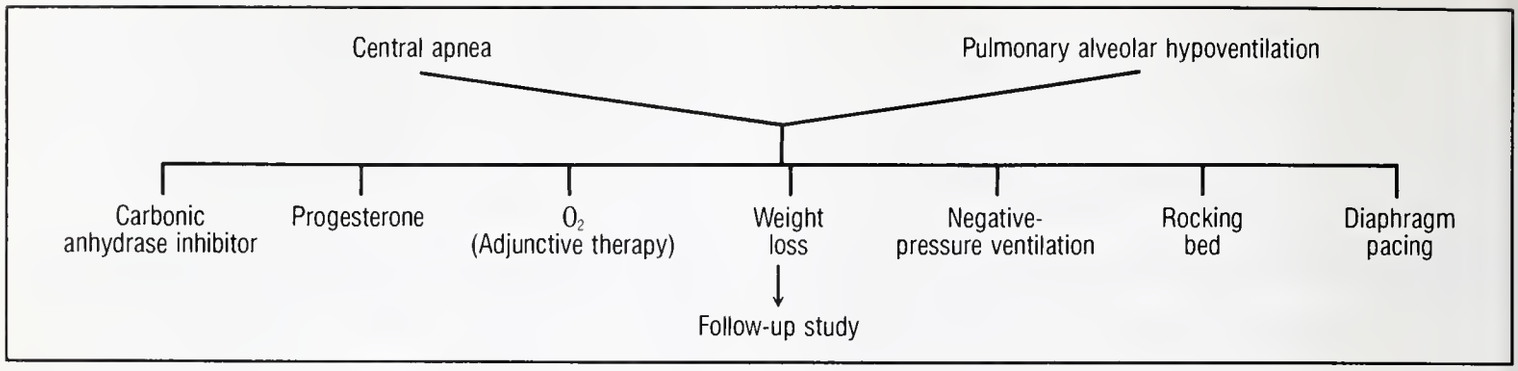

Figure 2.—Algorithm for treating central apneas and primary alveolar hypoventilation.

ample, hypothyroidism can be easily treated with thyroid hormone supplementation. Adenotonsillar hypertrophy may promote anatomic narrowing of the upper airway which can be treated with tonsillectomy and adenoid excision. Other anatomic abnormalities, such as micrognathia or retrognathia, may respond less predictably to surgical procedures such as mandibular revision. Such surgical correction should, of course, only be undertaken by a specialist with expertise in the procedure and its application to this group of patients.

Other surgical procedures are directed towards less clearly identified anatomic predispositions to upper airway obstruction. A permanent tracheostomy bypasses the site of obstruction, abolishing obstructive apnea and improving nocturnal oxygen saturation. We currently reserve this procedure for patients with potentially life-threatening arrhythmias or those for whom other therapies have failed (often due to poor compliance). Another surgical procedure is uvulopalatopharyngoplasty, which extensively revises the soft tissues of the oropharyngeal region. This can resolve upper airway obstructions and obviate the need for a tracheostomy. It must be emphasized that the success of this procedure has been extremely variable primarily due to uncertain criteria for proper patient selection.

A recently developed nonsurgical approach to these patients is the application of continuous positive airway pressure (CPAP) to the upper airway via a nose mask. Nasal CPAP has proved to be well-tolerated and effective in reversing obstructive apnea in several studies. Reasonably priced commercial CPAP units for in-home use by patients are currently available.

There are several medical approaches to the treatment of obstructive and mixed apneas. Weight loss may be effective in most patients, but this has proved difficult to achieve or sustain in this population. Respiratory depressants such as alcohol and sedatives should be avoided in these patients, as they have been well-documented to worsen obstructive sleep apnea. Nocturnal oxygen therapy will improve oxygen saturation during sleep and in as many as 40% of patients significantly reduces apneas. Due to the high cost of oxygen, it should be used only as an adjunct to other measures directed at improving alveolar ventilation. Progesterone, a respiratory stimulant, has been used with some success in some studies, but we have found it to be useful primarily in those patients also suffering from PAH. Protriptyline is a nonsedating tricyclic antidepressant we have used in the treatment of obstructive apnea with about 20% to 30% success. Therapy is typically initiated with a dose of 5 to 10 mg at bedtime but may be increased as needed to a dose of 30 mg. Patients should then be closely monitored for the appearance of side effects (insomnia, rash, urinary retention in men and so forth) that may be intolerable, especially at higher doses.

Figure 2 shows therapeutic approaches to central apnea and PAH. There are no surgical procedures currently indicated here, although electrical pacing of the phrenic nerve or diaphragm may be done in the absence of spontaneous respiration. We have found it unnecessary to use this procedure. Alternate mechanical approaches include the use of nocturnal negative-pressure ventilation and even the use of rocking beds. It should be remembered that in some patients with combined obstructive and central apneas, obstructive episodes may actually worsen during negative-pressure ventilation and these patients may, therefore, be considered candidates for nocturnal positive-pressure ventilation.

Medical approaches to these patients are more commonly used. Weight loss, although helpful, is again difficult to achieve or sustain in this population. Oxygen should again be used primarily as an adjunct to other measures designed to improve alveolar ventilation, although it has effected a cure in some patients with central apnea, presumably due to some respiratory stimulant effects. Progesterone has been successfully used to treat central apnea and primary alveolar hypoventilation, using a dose of 20 to 40 mg three times a day. Carbonic anhydrase inhibitors are also respiratory stimulants and have been found effective in some patients. Dichlorphenamide (Daranide) may be used in doses of 50 to 100 mg twice a day, while acetazolamide (Diamox) may be used in a dose of 250 mg four times a day. Theophylline is a well-known respiratory stimulant, used frequently with success in treating recurrent apnea of prematurity. Although some researchers report limited success using theophylline in the therapy for central apnea in adults, our experience with such usage has been generally disappointing.

After a tolerable therapeutic intervention has been initiated, symptoms and features typically seen with the syndrome should improve. A follow-up nocturnal polysomnographic study is usually indicated, however, at a later date to assess effects of therapy and to direct the physician towards further intervention if necessary.

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Primary Care Physician Satisfaction With Case Management

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Primary care case management is frequently proposed as one mechanism to reduce the overall cost of health services. This concept places a utilization control function upon primary care physicians who, under primary care case management, must approve all patient access to specialty physician services and hospital services. This utilization control function, often called the gatekeeper role, places new responsibilities on primary care physicians. In this study we surveyed primary care physician attitudes regarding their role as case managers.

(Davidson RC, Fox JE: Primary care physician satisfaction with case management. West J Med 1986 Aug; 145:251-253)

The cost of health care services in the United States continues to be a major concern. In 1983 US health care expenditures totaled $355.4 billion, with an average expenditure of $1,459 per person.[1] This was 10.8% of the gross national product, a percentage that continues to rise each year. The medical care component of the Consumer Price Index increased at an annual rate of 8.7% between 1982 and 1983, contrasted with an overall inflation rate of 3.2% for the same time period.[1]

Primary care case management is often proposed as one mechanism to control costs.[2] It places primary care physicians in the role of managers of health care services for the clients (patients) under their responsibility. This management role, often called the "gatekeeper role,"[3] usually is combined with financial incentives for a primary care physician to reduce the use of hospital and high-cost specialty services.[3-6] The management role calls for approval by a primary care physician before admission to hospital or specialty services are authorized by the plan.

Primary care physicians have traditionally provided an informal coordinating role of hospital and specialty services for patients under their care, but primary care case management introduces formal control mechanisms that are new. Although primary care case management continues to expand as a mechanism of cost control, primary care physician opinions about this new role have not been studied.

Physicians and Methods

To assess primary care physician satisfaction with the role of manager of specialty and hospital services, we surveyed the primary care physicians providing case management services under contract with a large, independent practice association in the Sacramento and northern California area. Foundation Health Plan (FHP) uses a primary care physician management system that requires that access to specialist services and all hospital admissions be approved by a plan primary care physician.

FHP was selected as the study plan for several reasons. First, it reimburses plan physicians on a fee-for-service basis with financial incentives to a primary care physician for controlling costs. Thus, capitation payment to the physician does not become a confounding variable in measuring physician satisfaction with primary care case management. Physicians enrolled in FHP are, predominantly, solo or small-group private physicians not part of large multispecialty group practices with built-in referral patterns. A third reason was that most of the participating physicians had practiced in the community on a fee-for-service basis without primary care case management before joining FHP and could therefore contrast their current role with their previous practice.

A questionnaire was mailed to every physician listed as a primary care provider in the categories of general or family practice and internal medicine. FHP also lists pediatricians and obstetrician/gynecologists as primary care physicians but they were not part of this study. Primary pediatrician use of hospital and specialty services is usually so low that their function as a case manager is quite different from primary care management of adults. Obstetrician/gynecologists were excluded because they are often a referral specialist for other primary care physicians, which could alter their opinion regarding primary care case management.

The questionnaire was sent to 266 primary care physicians of whom 147 returned the questionnaire for a 55% response rate. Because the questionnaire was not designed to identify

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the respondents, a validity check of nonrespondents could not be made. Thus, the degree of similarity of the two groups is not known. The responding physicians were asked to answer four questions regarding their practice and a series of questions regarding their satisfaction with their primary care case management responsibilities. Their responses were given on a Likert scale, with five steps ranging from strongly agree (+2) to strongly disagree (−2). A neutral response was 0. A satisfaction index was calculated for each question by averaging the responses on the numerical scale. One question was included as a validity check and is not reported in this study.

Results

Of the 147 questionnaires returned, 93 (63%) were from general or family practice physicians while 54 (37%) were from internists. The response rate for general or family practice physicians was 58% and for internists 51%.

The percentage of each physician's practice for case management services varied from less than 10% to more than 50%. Figure 1 illustrates the mix. Overwhelmingly (95%), the physicians felt the percentage of their patients enrolled in plans requiring case management would increase in the future. A third (32%) of the physicians felt that their willingness to provide primary care case management services had increased their patient population. Most (63%) felt it had helped to maintain their patient population, while only 5% felt the decision had decreased their patient population.

Physician responses to the four satisfaction questions showed a high level of satisfaction with their role as case manager, although they felt their specialty colleagues were less satisfied with primary care case management. Overwhelmingly (88%), the physicians felt that it is an appro-

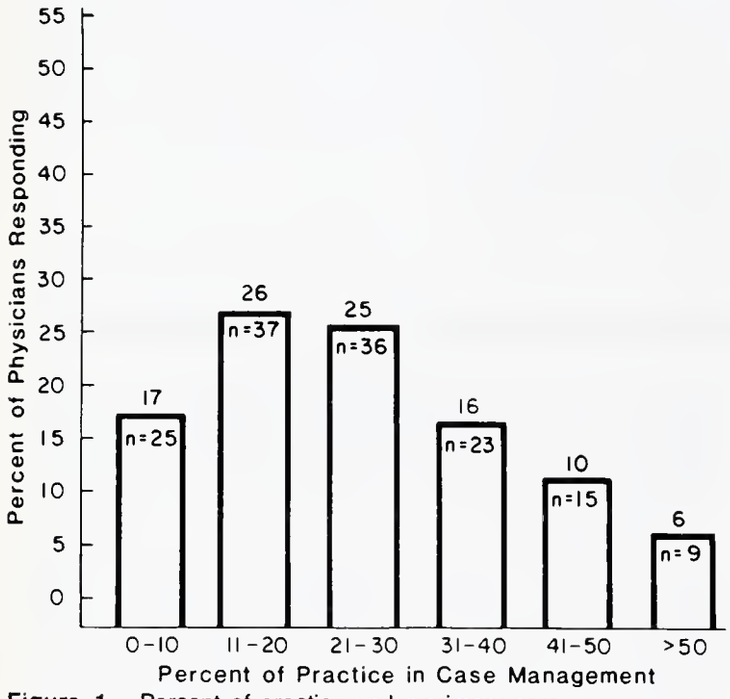

Figure 1.—Percent of practice under primary care case management.

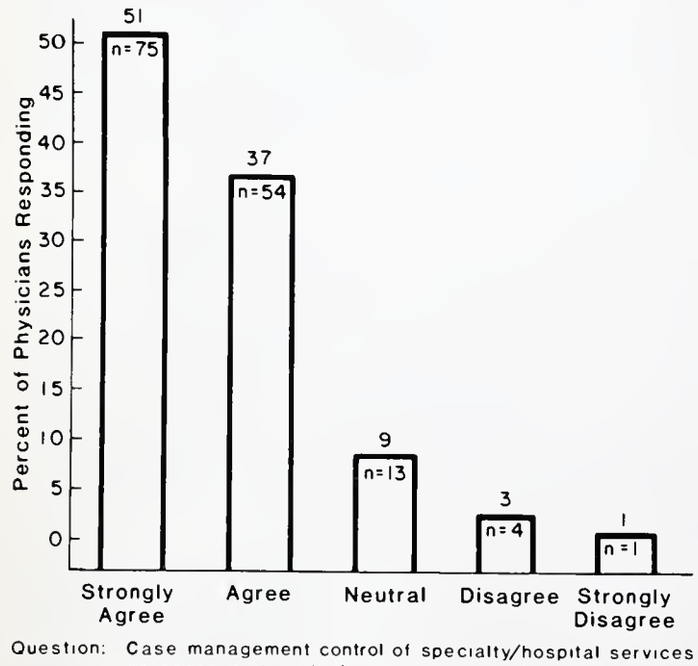

Figure 2.—Primary care physician response to the appropriateness of the role of primary care case management.

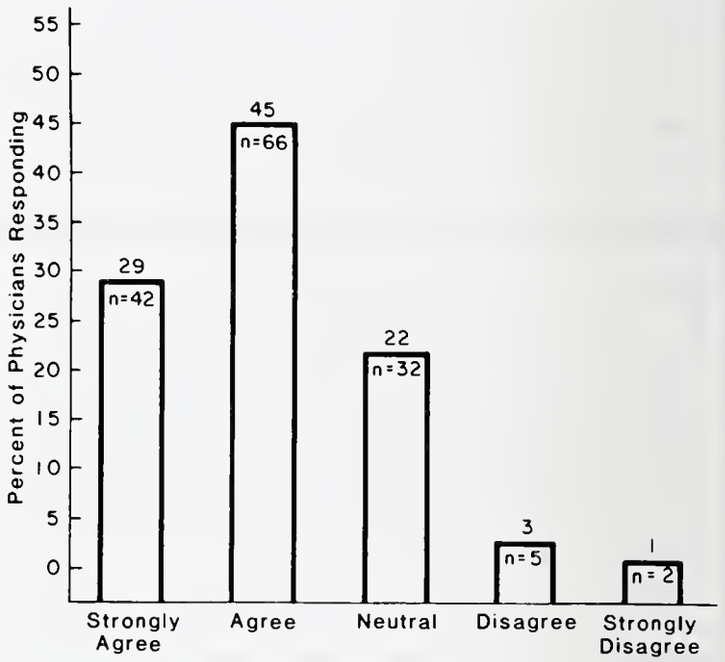

Figure 3.—Physician perception of patient satisfaction with primary care case management.

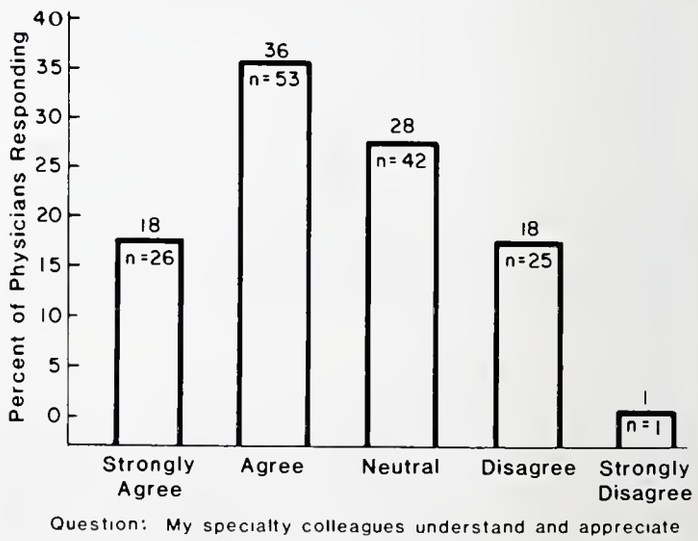

Figure 4.—Primary care physician perception of specialty physician opinion of primary care case management.

priate role for primary care. Figure 2 illustrates their response to this question. The satisfaction index for this question was a strongly positive +1.35.

Most primary care physicians also felt that their patients liked them to manage access to specialty and hospital services through case management. Figure 3 shows responses to the question of patient satisfaction with their case management role. The satisfaction index for this question was +0.96.

When the physicians were asked whether their specialty colleagues liked their role as case manager, the results were more mixed. Figure 4 shows their responses to this question. The satisfaction index, while still positive, was only +0.53.

The physicians responded that they did enjoy their role as case manager. Their satisfaction index for the question on enjoyment of primary care case management was +0.89. Figure 5 shows their responses.

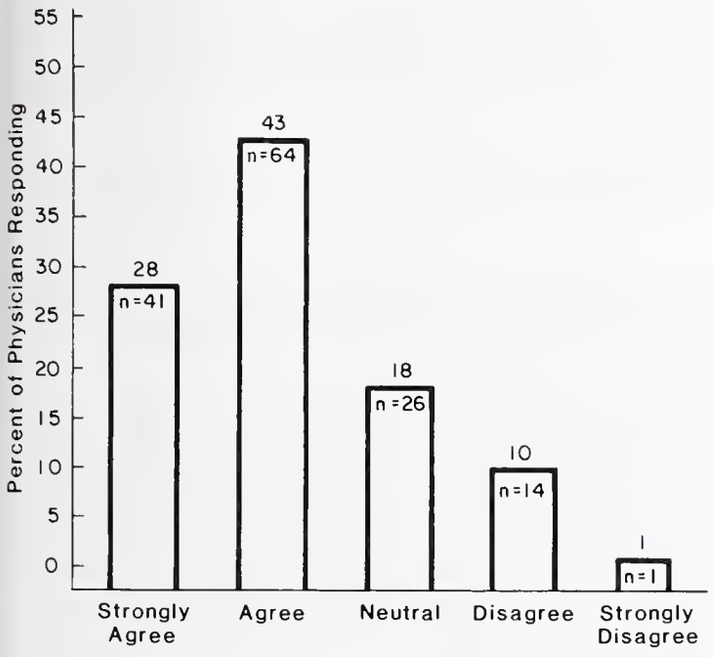

Figure 5.—Primary care physician satisfaction with primary care case management.

Finally, a comparison of the degree of satisfaction for these four questions between those physicians with a lower percentage of patients enrolled in a primary care case management plan (less than 20%) and those physicians with a higher percentage of patients in such a plan (more than 20%) was made. There was no significant difference in the response of these two groups to any of the four questions.

Conclusion

This study of primary care physicians serving as case managers in a large independent practice association on contract with a health plan showed a high level of satisfaction with this new role. The responses to all four of the satisfaction questions were positive, indicating an overall favorable response to their primary care case management role. The physicians were the most positive in responding that this was an appropriate role for primary care physicians and were the least positive in judging their specialty physician colleagues' satisfaction with primary care case management. As the use of primary care case management appears to be on the increase as a method of holding down health care costs, it is gratifying to find that, in general, primary care physicians will accept this new role and, indeed, seem to enjoy it.

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Gatekeeping—Clinical and Administrative Issues

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Most gatekeeper-based models of health care delivery utilize primary care physicians for authorizing services, screening referrals, managing cases and monitoring costs. Issues in four major areas related to gatekeeping have arisen in such systems: those affecting patients primarily, those affecting physicians primarily, those related to administering the gatekeeping function and, finally, those issues related to the health care system as a whole.

(Ellsbury KE: Gatekeeping—Clinical and administrative issues. West J Med 1986 Aug; 145:254-257)

One of the fastest growing segments in the health care economy is the prepaid system or health maintenance organization (HMO) based on the primary care gatekeeper. Luft sees the role as essential to the concept of the HMO and that "the major issue with respect to specialists is the extent to which an HMO limits access to specialists through maintenance of control through the primary physician."[1] Somers defines the gatekeeper as a "designated health professional who serves as the patient's 'primary physician' and refers the patients to specialist services, as needed, as a condition of third party payment for such services. While capitation is an appropriate method of paying for the gatekeeper function, other methods are acceptable, provided the rates are fixed for a defined period of time."[2] She reviews the parallels between the emerging gatekeeper-based system in the United States and the National Health Service in Great Britain and other European health care systems where patients are registered with a general practitioner who has the authority to authorize or deny referral to specialists.

Typical gatekeeper-based systems are characterized by such features as the following:

- Prior authorization by the gatekeeper for referrals, procedures and hospital admissions.
- The primary care physician role as case manager, coordinating the work of consultants and screening out unnecessary specialty consultations and hospital admissions.
- Monitoring by the gatekeeper of information about costs and referral patterns.
- Emphasis on comprehensive, coordinated and continuous care as responsibilities and not just philosophical goals of a primary care physician.[3]

In most gatekeeper-based systems, patients pay a fixed premium for their health care and any money left over after delivery of that care is distributed to physicians or to the prepaid system to cover administrative costs. Usually some type of "pool" is reserved within the participating group, based on premium collections, to be used in high-cost cases. Typically, this is 10% to 20% of the total premiums collected. A "stop-loss clause" provides that if caring for a patient costs more than a certain amount (about $5,000 in a given year), the HMO will cover the costs of the care and the physician does not have to deplete the "shared-risk pool" beyond a certain limit. Usually there are separate stop-loss limits for inpatient and outpatient care. If the inpatient pool has an excess, it is usually applied to meet deficits in the outpatient pool and vice versa. By this mechanism, physicians share in the financial risk of providing health care.

Many efforts to control health care costs have focused on the physician as "captain of the health care team." One study reported that 50% to 80% of health care costs are physician controlled.[4] In a survey by Catlin and co-workers of 104 non-independent practice association HMOs, 28% of which were staff-model HMOs and 67% network-model HMOs, 70% of the responding HMOs rated the gatekeeper function very important, especially those HMOs whose hospital admission rates were high; 77% of the HMOs relying mainly on primary care physicians rated gatekeeping very important.[5]

Many gatekeeper-based HMOs are independent practice associations (IPAs), which tend to allow more "out-referrals" (referrals outside the HMO) than do staff-model HMOs. For this reason (and others), premiums and costs are often higher in IPAs than in other types of HMOs.[6] Some HMOs may attract sicker patients who are interested in obtaining care from specialists participating in the HMO, thus accounting for the higher costs of care. Because of the heterogeneous nature of physician practice styles and because of the

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ABBREVIATIONS USED IN TEXT
AUP = Association of University Physicians
HMO = health maintenance organization
IPA = independent practice association

decentralized structure of such HMOs, they require strong administrative support, effective data management, adequate review of practice style and careful attention to such controls as second opinions and mechanisms for discontinuing affiliations with physicians who do not practice cost-effective medicine.[6,7]

There is some evidence that the primary care gatekeeper function does control costs. In Hunterdon, New Jersey, hospital admissions and costs increased when specialists were given more control and primary care physicians were taken out of the gatekeeper position.[8] At the University of Washington, the SAFECO-sponsored United Health Care plan spent $221 per year per outpatient managed by the gatekeeper, as compared with $250 for patients covered under the same plan but with no gatekeeper, mainly due to lower utilization of services and fewer specialist consultations. More than half the primary care physicians in the plan collected surplus payments from the plan, averaging $413 per physician.[9] The average deficit per physician was $169, with a maximum of $1,833 paid back per physician.[10] In Catlin's survey of 104 HMOs, those with lower hospital admission rates relied on gatekeepers and had fewer physicians per 1,000 members. Ambulatory service utilization was lower in the HMOs with low physician/patient ratios.[5] In Wisconsin, physicians reported that serving in a gatekeeper role made them much more aware of health care costs.[11]

Smith[12] describes the affiliation of the Family Practice Center in Akron, Ohio, with an IPA linking 19 practice sites, with the goal of educating residents, increasing patient volume, teaching cost-effectiveness and studying utilization patterns and patient satisfaction among prepaid and fee-for-service patients. Burkett reported on an IPA where referral rates and hospital admission rates were lower for family physicians and pediatricians than for internists.[13]

Since 1982 the University of Washington's physician practice group, the Association of University Physicians (AUP), has participated in HealthPlus, a network-model HMO and subsidiary of Blue Cross of Washington and Alaska. This plan enrolls 2,201 subscribers, 1,295 of whom have selected a personal care physician; 66% of those with a personal care physician are assigned to the Family Medical Center; 49 faculty physicians act as personal care physicians in a gatekeeper role as defined above. The bulk of the other AUP HealthPlus patients are assigned to primary care internal medicine faculty and a few to faculty obstetricians and pediatricians. During the three-year history of this gatekeeper-based HMO at the University of Washington, many dilemmas have arisen for the primary care physicians. I will discuss some of those issues.

Case examples and discussion are adapted from actual patient problems presenting in the Family Medical Center at the University of Washington. The issues associated with gatekeeping can be grouped into four major areas: those affecting patients primarily, those affecting physicians primarily, those related to administrative functions and those issues related to the medical care system as a whole.

Patient-Related Issues

Gatekeeping issues affecting patients primarily can be summarized as follows:

Discrepancies Among Insurer's Promised Benefits, Patient Expectations and Physician Perceptions of What Is Medically Indicated

Case. A 33-year-old woman has shakiness, dizziness and anxiety following meals, with an inconsistent pattern and with no correlation to food type. She requests allergy testing by a friend's allergist. The allergy consultant within the primary care provider's medical group advises against such testing because of inaccuracies of the technique. The patient reminds the primary care physician that the insurance program assured her by phone that allergy testing is a covered benefit.

From Mayer's study[14] of referral patterns in a capitation-type HMO based in a multispecialty group, he concluded that many patients may join HMOs precisely to obtain care for conditions for which other insurers may exclude coverage or which might require a copayment. The clinic he studied had few barriers to referral, however.

Workups for conditions like allergies, infertility, rheumatologic disorders and neurologic disorders are very costly, with many new or experimental techniques, especially at tertiary care centers. Many insurers are vague about specific benefits, leaving the decision about details of the workup to the involved physicians. Assuming that the procedures may be elective and not medically necessary, the gatekeeper holds considerable influence over the extent of the workup.

The Care-Giver Role May Conflict With the Cost-Saving Role

The gatekeeper protects a limited pool of resources and can reap economic benefit from any remaining surplus. This has the potential to compromise quality of care if there are not adequate quality assurance mechanisms. In Mechanic's words, "Capitation, in the absence of peer evaluation and rewards, may result in undesired behavior such as limited professional commitment and lack of responsiveness to patients."[15] The recommended consultant or the vendor whose services are covered under a gatekeeper-based system may not be the best one available.

Physician-Related Issues

The gatekeeper problems primarily affecting physicians include the many issues related to collegial relationships.

Difficulty Controlling Services Performed By Consultants

Case. A 27-year-old man has chronic diarrhea after several courses of optimal medical therapy for documented *Giardia* infection. He requests referral to a gastroenterologist. The gastroenterologist undertakes a workup that includes multiple endoscopies and biopsies, intestinal absorption studies and laboratory and microbiologic studies. Much of the workup is under way before the consultant contacts the gatekeeper. The bill totals $3,000. No cause is found and in the end the patient's diarrhea responds to symptomatic treatment with antimotility agents, as originally initiated by the primary care physician.

The gatekeeper managing such a complex, expensive case occupies a difficult, often uncomfortable role. Catlin says that

"the role of the gatekeeper is not the most satisfying aspect of the work of a family physician"[5] and Stephens assesses the tasks of triaging and utilization review as "objectionable."[16] Many primary care providers are quite happy with the increased control the gatekeeper role offers them, but others are uncomfortable with the role of rationer and "policer," resenting the increased paperwork.[11]

Interspecialty conflicts may arise when primary care providers deny authorization for services provided by specialists. This can be exacerbated by the gatekeeper's lack of professional status, lack of knowledge or prior established referral patterns in the community. In the Hunterdon, NJ, HMO, specialists resented the primary care giver in the gatekeeper role and took over that role for themselves.[8] Opposition to the gatekeeper function has arisen in such fields as dermatology, where the concept has been labeled monopolistic and anticompetitive,[17] inefficient and in the long run more costly.[18] Primary care departments have to weigh the risk of political isolation from other departments if they "refer outside the system" or push for lower fees on behalf of a reimbursement scheme that comprises only a small portion of their patient care volume.

Cost control after consultation requires strong administrative support and is more difficult if consultants are paid on a fee-for-service basis. This problem was a key element in the demise of the SAFECO plan in Seattle where consultant fees consumed much of the premium, and funds in the shared-risk pool became "no one's responsibility."[10]

A related problem is that of secondary referral of patients by one specialist to another specialist. Eisenberg proposes that hospitals and consultants be "enlisted as collaborators" in cost containment, increasing the incentives for specialists to control unnecessary costs.[3]

Conflicts Between Short-Term and Long-Term Goals

Case. A physician seeing a 55-year-old woman for health maintenance usually follows a clinic protocol that recommends a mammogram for women older than 50 years. The physician pauses when becoming aware that the patient is on a prepaid plan, knowing that the test costs $105 and, if applied now to all women older than 50, will consume most of the yearly capitation allotment for such patients and will reap benefits for patients who in five years may not even belong to the same health plan.

Performance reports deal in terms of months and quarters. Morbidity and mortality, especially when related to chronic disease and prevention, occur over time spans of years or decades. Preventive services such as mammography and colon cancer screening may be pursued less vigorously in a capitation-based system, especially if performance reports indicate that physicians are generating too many costs in a given short-term period. Institutional protocols supported by medical directors and administrative expectations such as those developed by many staff-model HMOs may reduce the tendency to short-change prevention efforts.[9]

Administrative Issues

Implementation and Education Issues

Administrative support requirements for gatekeeping differ from those needed for traditional fee-for-service practice. Smith's study estimated that monthly administrative costs would total a remarkably low $265.39 for 500 IPA patients enrolled on a capitation basis in one family practice center. He estimated that these costs were more than offset by the high collection rate and lack of billing costs.[12]

Eisenburg and Williams found that educational efforts must be coupled with administrative and structural changes—that is, peer review with educational feedback or financial penalties or administrative changes with financial penalties. Their conclusions emphasize financial incentives as a mechanism of change—incentives central to the gatekeeper function.[19]

Meier and Tillotson cite numerous studies showing that physician behavior in IPAs can be altered with economic incentives from surplus pools or possible loss of patient volume and income. Behavior is easier to modify in smaller groups where goals are internally consistent and where communication is effective.[6]

In efforts to educate physicians about costs, the motivations behind physician generation of health care costs—fear of malpractice, peer pressure, type of training, personality, practice structure, curiosity and lack of knowledge, among others—must be recognized.

Difficulties Determining the Proper Capitation Rate

The University of Washington has a higher proportion of the HealthPlus (prepaid) patients who are women between 20 and 40 years of age than do the other participating medical groups in the HealthPlus network; because the utilization rate in this group is higher than average, the capitation rate is increased for the university-based practice relative to other participating medical groups. The unpredictability of service utilization and referral patterns creates difficulties in making financial projections. Early experience at the University of Washington indicates that many patients are drawn to the university for such services as infertility benefits and care for chronic diseases such as cancer and rheumatoid disorders.

Difficulty Deciding Who Should Act as Gatekeeper

Typically the management of a prepaid plan determines what specialties will be placed in gatekeeper roles. Specialties qualifying as gatekeepers may change as the plan evolves. An oncologist gatekeeper may be appropriate for a patient with cancer. A nephrologist may best service a patient with a chronic renal disorder.[1] Aiken and associates argue that specialists do indeed deliver a considerable amount of "primary care" in their practices,[20] though their findings have been disputed.[21] Eisenberg, in discussing the role of the internist as gatekeeper, concedes some of the deficiencies in training of internists for such a generalist role, pointing to their weaknesses in such areas as ophthalmology.[3]

Health Care System Issues

Potential for Multitiered Medical System

There is a potential for a multitiered medical system if the poor, who can afford only lower cost medical coverage, are limited to a gatekeeper-based medical plan. There is little evidence that restrictions on referrals compromise quality of care. Thurow predicts that prospective payment will become the dominant form of reimbursement in the United States and that a three-tiered medical system will develop, the lowest serving the poor and elderly, the middle serving corporate

employees and the top tier serving those who can afford free-market rates. Physicians will tend as a group to compete to care for consumers in the top tier.[22]

Conflicts Between Financial and Legal Liability

Case. A newborn was noted to have a systolic ejection murmur with no other problems and a normal electrocardiogram and chest film. The mother's pregnancy had been complicated by preeclampsia, a prolonged antepartum stay and many conflicts with health care providers over delivery plans. She had on occasion asked to read her chart and had refused to let one physician in the practice see her on rounds. The baby's heart murmur was considered benign but because of concerns about medicolegal complications, her personal care physician requested a cardiology consult that would otherwise probably not have been ordered.

The high cost of defensive medicine is very real when a physician sees the immediate result of ordering an extra test or consultation "to be sure" or consulting a specialist to back up a decision that carries a risk of complication, either medical or legal. What is medically elective in one situation may be "standard of practice" and thus "medically necessary" or prudent in another situation.

This discussion and case examples touch on some of the many issues related to the gatekeeper model of health care delivery. New modifications will arise, and the number of coverage options will multiply. The days of "carte blanche" medicine and retrospective reimbursement are over. During this period of rapid change, many difficult adjustments will need to be made. The effect economic changes such as the gatekeeper model have on patient care, professional relationships and distribution of medical care deserves further study by both providers and administrators.

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Capitation in California—An Analysis of At-Risk Financing of Medicaid Services

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Recent legislative changes have fostered the growth of a highly competitive health care market in California. In addition to selective hospital contracting for Medicaid (Medi-Cal) services, the California Medical Assistance Commission is attempting to initiate pilot projects to capitate Medi-Cal beneficiaries in selected geographic areas throughout the state. Selective contracting with county capitated organized health systems is also underway in Santa Barbara County, with plans for other counties on the drawing boards. This paper describes these capitated programs as well as addressing problems that may arise in this transition from a fee-for-service to a capitated Medi-Cal system. Specifically considered are issues related to underutilization, quality of care, implementation, eligibility and effects on existing patterns of care.

(Halfon N, Newacheck PW: Capitation in California—An analysis of at-risk financing of Medicaid services [Medicine and Government]. West J Med 1986 Aug; 145:258-262)

The continuing revolution in health care financing is having significant impact on the organization of health care services in California. A veritable alphabet soup of new organizational forms are springing up: health maintenance organizations (HMOs), preferred provider organizations (PPO), individual practice associations (IPAs), exclusive provider organizations (EPOs) and primary care networks (PCNs). For-profit and not-for-profit corporations are entering the health care marketplace, with a variety of marketing schemes designed to capture an increasing percentage of the market share. New competitors in California's fragmented health care market have brought with them alternative delivery sites, utilization review organizations and new third party administrators.[1] Furthermore, many recent legislative initiatives are aimed at increasing competition in the health care marketplace by deregulating the insurance industry, encouraging competition among hospitals for Medicaid (Medi-Cal) patients, and by encouraging the development of capitated health systems.[2]

As both public and private sector payers become increasingly aggressive in their cost-containment strategies, risk is being shifted from the payers to the providers and to the consumers. The passage of the Omnibus Budget Reconciliation Act (OBRA) in 1981 set the stage for risk-shifting options within the giant Medicaid system. Section 1915 of OBRA allows the Secretary of Health and Human Services to waive the requirements of Sections 1902 and 1903 of the Medicaid statute that prohibited states from contracting on an at-risk basis. Section 1915 allows states to seek waivers to (1) implement case management systems, (2) allow local governments to serve as brokers by assisting Medicaid recipients in choosing among competing health plans, (3) provide Medicaid recipients additional and otherwise uncovered services for enrolling in cost-effective plans and (4) implement prudent buyer systems.[3]

With the passage of OBRA, states have applied for waivers from the Health Care Financing Administration and have created three types of model demonstrations: the competing health plan model, the health insuring organization (county at risk) model and the partial capitation model. The competing health plan model uses competition among health maintenance organizations to reduce health care costs. After obtaining the appropriate waiver, states can require all Medicaid beneficiaries in a particular area to join one of the competing HMOs. At present there are nine counties in six states utilizing this model. The health insuring organization (HIO) model allows the state to contract with a county government on an at-risk basis. The county HIO does not actually provide care like an HMO but rather arranges, administers and pays for care. This model of care is currently used in Santa Barbara

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ABBREVIATIONS USED IN TEXT

AFDC = Aid to Families with Dependent Children
CDHS = California Department of Health Services
CMAC = California Medical Assistance Commission
ECP = Expanded Choice Program
EPO = exclusive provider organization
HIO = health insuring organization
HMO = health maintenance organization
OBRA = Omnibus Budget Reconciliation Act

County, California. In both the HIO and competing HMO demonstration projects, enrollment of beneficiaries has usually been mandatory.[4]

In California the same legislation (AB 799) that authorized competitive bidding of Medi-Cal hospital rates and the institution of the California Medical Assistance Commission (CMAC) in 1982, also authorized the Commission to develop pilot-capitated demonstration projects in selected counties. These projects could eventually phase out fee-for-service payment for Medi-Cal and replace it with capitated systems, using either the county HIO or the competing HMO models. Under capitation, providers of Medi-Cal services receive a fixed amount of payment for each eligible person enrolled in their plan, regardless of the actual costs incurred in providing medical treatment. Hence, the provider is "at-risk" in a financial sense.

The current philosophy of many California leaders favoring competition grew out of a combination of factors: (1) California's fiscal crises in the early 1980s, (2) rapid increases in Medi-Cal spending, (3) the perceived failure of regulation and (4) an emerging procompetitive marketplace fueled by a rapid increase in physician supply, as well as the growth of HMOs as major providers and insurers. Furthermore, the current administration has expressed a desire to convert Medi-Cal to an at-risk capitated delivery system. The key features of the administration's plan include slow phase-in over a decade; selection and assignment of eligibles in order to reduce adverse selection; negotiation, contracting and management functions to reside within the Department of Health Services, not in CMAC; enrollees "locked in" to plans for one year; Knox-Keene licensure for plans prior to getting contracts.

The remainder of this paper addresses the development of these Medi-Cal at-risk capitated programs in California, and discusses anticipated impacts and potential concerns for Medi-Cal eligibles.

"Expanded Choice"

The Expanded Choice of Health Care Plans (Expanded Choice) is a joint pilot project between CMAC and the California Department of Health Services (CDHS). Under the proposed arrangement CMAC would be responsible for the design of the pilot project, negotiation of contracts and devising contract and program regulations. CDHS would be responsible for the actual implementation of the program. Expanded Choice was envisioned as a pilot-demonstration project to test the application and feasibility of providing health services for Medi-Cal beneficiaries through competing HMOs. Before implementing Expanded Choice the state had 13 health maintenance organizations under contract. As of January 1985 these HMOs provided care to approximately 8% of Medi-Cal eligibles, primarily in Los Angeles County. They are currently providing care to Medi-Cal beneficiaries on a *voluntary* enrollment basis. Under the proposed Expanded Choice Program (ECP) enrollment in an HMO would be *mandatory* for most Medi-Cal eligibles living in each of the target geographic areas.

CMAC was authorized to choose at least two and no more than six geographic areas to implement Expanded Choice. After an extensive application process, in April 1985 CMAC decided to implement ECPs in San Diego County, San Fernando Valley (Los Angeles County) and Stanislaus County. If all three programs had become operative, approximately 20% of the current state Medi-Cal population would be covered in the ECP. CMAC was restricted by the terms of its federal waiver to this 20% level.[5]

Selection of target areas was initially based on the percentage of Medi-Cal eligibles receiving inpatient services, average monthly Medi-Cal expenditure per enrollee and availability of a sufficient number of federally and state qualified HMOs in each area to provide adequate access to beneficiaries. Once the state contracted with a sufficient number of HMOs in these areas, it planned to phase out the fee-for-service option. Most, but not all, eligibility categories would be included in the ECP: Medically Needy Share of Cost, Medically Needy Long-term Care No Cash Grant, Medically Indigent Children, Medically Indigent Adults, Renal Dialysis and Refugee-Entrants would continue to be served through the fee-for-service system. Some services would also be excluded from the ECP, and would continue to be available through the statewide fee-for-service Medi-Cal program. These include Child Health and Disability Prevention services, dental services, mental health services, Adult Day Health Services, Multipurpose Senior Service Programs, acupuncture, chiropractic services, podiatric services and healing by prayer or spiritual means.[5]

Several criteria were to be used to select participating HMOs. These include the following:

- acceptance of capitated rate for enrollees (95% of projected fee-for-service expenses);
- qualification for state licensure (Knox-Keene);
- fulfillment of federal Medicaid requirements;
- provision of a standard minimum package of covered services;
- willingness to contract with the state;
- willingness to subcontract with individual noninstitutional providers of care, community clinics and county health systems when appropriate;
- ability to deliver services in an acceptable fashion.

Since all HMOs participating in the Expanded Choice Program would be subject to the provisions of the Knox-Keene Health Care Services Plan Act, all plans need acceptable quality assurance, peer review and grievance procedures in place before an operating license is granted. Furthermore, the Waxman-Duffy Act requires that the Department of Health Services conduct an annual comprehensive review of each participating HMO, including examination of cost, utilization, quality and grievance records. In addition, two advisory panels made up of local citizens and Medi-Cal beneficiaries would be constituted in each closed area to review utilization patterns. A Beneficiary/Community Advisor

Board made up of local citizens and Medi-Cal beneficiaries would monitor beneficiary appeals and complaints and monitor each contract plan's grievance procedures to assure that they are operationally adequate. A provider advisory board made up of both physician and nonphysician Medi-Cal providers would review each plan's utilization patterns to assure that all necessary services, including ancillary services, are available in each of the contract plans.

Throughout its development, the Expanded Choice Program has been criticized by political opponents as well as health care providers.[6-8] The chairman of CMAC, Richard Silberman, has defended the program as a necessary experiment designed to improve public confidence in state funded health care and to insure a place for the Medi-Cal beneficiary in an increasingly competitive market.[9] Nonetheless, although programs were supposed to begin in both San Diego and the San Fernando Valley in 1986, followed by Stanislaus County in a subsequent year, the entire project has now been put on hold.

In the proposed San Fernando Valley Project, stumbling blocks were encountered at nearly every step. Many HMOs were not interested in participating in the pilot project. Approximately 950 valley physicians currently providing care for Medi-Cal beneficiaries would be required to form HMOs or subcontract with existing nonreceptive plans. In addition, opposition came from community and consumer groups. Public outcry was sufficient to convince local legislative representatives to encourage the introduction of restrictions into the 1986-1987 budget to prevent CMAC from using funds to implement the Valley ECP.

In San Diego, planning and implementation were ostensibly much smoother. A total of 10 HMOs from a field of 16 competitors were awarded contracts in the spring of 1986. The enrollment contractor was set to begin contacting eligible persons on June 15, 1986, when a legislative conference committee eliminated $40 million needed to implement ECP in San Diego. Reports in both San Diego and Los Angeles newspapers suggested that the funding allocation died because of opposition by the California Medical Association lobby, the absence of strong program advocacy within CDHS and a growing lack of resolve on the part of the administration. Implementation of ECP in San Diego would have moved, by choice or assignment, approximately 160,000 of the 190,000 Medi-Cal-eligible county residents from fee-for-service to one of the ten HMOs. Although the program as originally planned is now defunct in San Diego, the Office of Capitated Health Systems is attempting to salvage the interest and potential participation of some of the HMOs.

County-Capitated Health Systems

The state of California is also pursuing contracts with counties to serve as health insuring organizations (HIOs) to Medi-Cal recipients through the creation of organized health systems (OHSs). In 1983 programs were authorized in both Monterey and Santa Barbara Counties. The Santa Barbara County program continues to operate but the Monterey County plan ceased to function after 20 months. In addition, an organized health system is scheduled to begin operation in San Mateo County this summer and the state is currently considering the requests for county organized health systems in Orange, San Bernardino and Ventura counties.

The Santa Barbara Special Health Care Authority began operating the Santa Barbara Health Initiative in September 1983 and has assumed responsibility for most Medi-Cal beneficiaries living in that county. With the exception of emergency services, all health services provided to enrolled Medi-Cal recipients are obtained through contracting providers. The central feature of this plan is a primary care network in which the primary care physician (case manager) is responsible for the provision of primary care, as well as the coordination and authorization of other needed medical services. The primary care provider serves as the gatekeeper and is required to authorize hospital admissions and referrals to specialists. Although beneficiaries are initially free to choose their primary care provider, once chosen the beneficiary is locked-in to that provider. This lock-in process is purported to be the most efficacious way to stabilize the links between providers and beneficiaries, improving patient education and preventive health while decreasing administrative costs.

Under this program the primary care physician shares financial risk (and potential gains) with the county for all services provided.[10] However, the physician is not at risk for the entire amount. Under the Santa Barbara system, 80% of the capitation funds are allocated directly to the participating primary care providers and 20% are held in reserve to serve as a trust fund for potential overruns on hospital care or specialty services. This 20% in reserve is used to offset all or part of any deficit incurred for these services. Therefore the provider is only at risk for 20% of the entire capitated payment.

Any residual left in the trust fund at the end of the year is split among the providers. The Santa Barbara Health Initiative has established fiscal viability by operating at 95% of projected fee-for-service expenditures (an estimated savings to the state of $900,000 in 1983-1984). More than two thirds of the participating primary care physicians received combined payments totaling more than $1 million, based on surpluses generated in the first year of operation.[10]

The Monterey Health Initiative began operations in June 1983 and by May 1984 had cost overruns that interfered with their ability to pay providers, and a deficit approaching $3 million. Several reasons were suggested for these cost overruns. Perhaps the most important was that the providers were reimbursed on a fee-for-service basis and, unlike the Santa Barbara plan, were at no appreciable financial risk if cost of care exceeded the amount of money allocated. Other causes including a low capitated payment rate from the state and inadequate management and information systems have also been suggested to explain the lack of financial viability. Although steps were underway to rectify these problems, the program closed in February 1985.[11]

Although CMAC intends to implement the HIO in San Mateo County, plans for Orange, San Bernardino and Ventura Counties have become less clear. The 1986 Consolidated Omnibus Budget Reconciliation Act (COBRA) has stipulated that HIOs must meet certain requirements previously set for HMOs: all HIOs must enroll a minimum of 25% non-Medicaid beneficiaries (75:25 enrollment mix ratio) and provisions must allow for disenrollment to another plan—that is, no lock-in. Although the San Mateo HIO would be exempted from these provisions for the duration of its waiver, new plans must comply with these regulations.

HMO Enrollment Trends

During January 1985 there were 2.85 million persons or 11% of California's population who were certified as Medi-Cal eligible. Of those eligible, 220,000 or about 8% were enrolled in 13 contracting HMOs. While the number of Medi-Cal eligibles enrolled in HMOs remains relatively small, growth in HMO enrollment has been substantial. Between January 1981 and January 1985, HMO enrollment of Medi-Cal eligibles rose 67%, despite a reduction in total certified eligibles statewide.

Increased enrollment of mothers and children (under the Aid to Families with Dependent Children [AFDC] Cash Grant and Medically Needy programs) accounts for almost the entire increase in HMO membership during the 1980s. Medi-Cal AFDC eligibles account for more than 93% of current HMO enrollees and are ten times more likely to be enrolled in HMOs than are Aged eligibles, and five times more likely to be enrolled compared with Blind and Disabled eligibles. Since families eligible for the Medi-Cal program are composed primarily of children, the HMO program is primarily a children's program; more than 66% of all HMO enrollees were under age 20 during January 1985[12] (unpublished tabulations from the Medical Care Statistics Unit of the California Department of Health Services).

Critical Issues

The rapid rise in HMO enrollment over the past four years pales in comparison to expected growth over the next few years. If and when the Expanded Choice Program becomes fully operational, HMO enrollment is projected to increase at least two-fold over 1985 levels. If the county HIOs continue to expand, additional beneficiaries will be capitated through this arrangement. The eventual outcome of these organizational changes on the delivery of health services is far from clear. These "at risk" or capitated systems may create financial savings for the Medi-Cal program, and they may serve to increase access to services for Medi-Cal recipients who live in areas where few providers currently participate in the Medi-Cal program. Under optimal conditions HMOs could deliver better preventive services and improve continuity of care. However, many observers are concerned that the state's drive to contain costs through these programs may result in reduced access to needed services for California's low income population and provide an inferior quality of care. Several critical issues must be considered during this transition from the fee-for-service system to capitated systems: underutilization, quality of care, implementation, eligibility and effects on the existing patterns of care.

Underutilization

When providers are placed at increased financial risk, economic incentives exist to restrict utilization of services, particularly those of an elective nature. Monitoring underutilization is a tricky and difficult task, and adequacy of care cannot be measured easily with standard auditing techniques. If less than a medically appropriate level of services is provided, the provider may benefit financially over the short term. However, over the long term the patient's condition may be aggravated, eventually resulting in higher than necessary treatment costs. Appropriately monitored long-term contractual commitments by providers might help to ensure that adequate preventive and routine services are provided at appropriate intervals rather than postponed.

Quality of Care

Although Knox-Keene licensure for HMOs is a necessary safeguard to ensure certain quality assurance procedures, the enforcement of Waxman-Duffy regulations could be more variable. Some critics have suggested that neither Knox-Keene nor Waxman-Duffy regulations are adequate to ensure quality care and, in addition, on-site audits might also be necessary to guard against underutilization and ensure appropriate use of referral procedures.[13] Gatekeeper systems, such as the Santa Barbara Health Initiative, by placing a physician at-risk financially for all services provided to an enrollee, regardless of who provides them, create additional uncertainties. This approach provides an economic incentive for the primary care physician to provide services that ordinarily might be provided by specialists under referral. The impact of such incentives on physician behavior and, ultimately, on quality of care are unknown. Monitoring such potential abuses is clearly difficult.

Implementation

The state already has the authority to continue to capitate the Medi-Cal System on a project-by-project basis without additional legislation. However, additional legislation may be crucial to ensure that implementation is judiciously planned and sufficiently monitored. The failure of Monterey County to successfully implement a capitated system has been partially attributed to poor planning, inadequate phase-in time and insufficient medical information monitoring systems.[11] Timely and accurate data will be necessary from the California Department of Health Services in order to provide useful planning and evaluation data for individual plans. In the past, CDHS's abilities to acquire, process and provide timely analysis have been somewhat limited. In addition, during implementation attempts must be made to ensure continued access to ancillary services that may remain in the fee-for-service sector.

Eligibility

Since risk-pool management under capitation relies on averaging periods of high use with those of low use, financial viability may necessitate extended eligibility periods rather than the traditional month-to-month eligibility determinations. So far the state has not authorized the use of a federal waiver of month-to-month eligibility determination. If the potential for improved continuity of care is to be realized, periods of extended eligibility must be considered. Furthermore, enrollment information systems must be linked to eligibility decisions in order to diminish the likelihood of retroactive denials of capitation payments. This will be further complicated under the Expanded Choice Program where beneficiaries can switch plans monthly. Eligibles must also be assigned to different providers in ways that minimize adverse selection but permit as much choice as possible. Additional monitoring systems will be needed to assess case mix/severity of enrollees for each plan in order to guard against adverse selection—that is, sicker eligibles with higher utilization patterns gravitating toward one particular plan or set of providers. Furthermore, the current eligibility determination process, based on county of residence rather than being state-

wide, might inhibit access and increase administrative costs, particularly where normal patient flow patterns overlap adjacent counties.

Impact on Existing Patterns of Care

A massive reorganization of Medi-Cal, such as envisioned by the state, could have additional important impacts on patients and providers of health services. First, university medical centers, children's hospitals and other tertiary care facilities that deliver regional high intensity care may not survive a simple capitation approach. These centers offer highly specialized services, and their risk pools often consist of multiple counties and sometimes the entire state. Adjustments must be made so their services are efficiently utilized, and so that they remain financially capable of providing needed services. Second, many minority physicians may not be included in the HMOs that are bidding for Medi-Cal contracts, even though they are often long-time providers of culturally relevant care to Medi-Cal beneficiaries. Third, there are several existing programs which serve this same population that might not be easily included or excluded from either the competing HMO or county HIO models. California Childrens Services, the Child Health and Disability Program and the soon to be implemented Comprehensive Perinatal Services do not fit easily into these capitated projects. These are special programs targeted to meet the needs of highly vulnerable populations and should not be compromised simply on fiscal or administrative grounds.

Conclusion

At the present time the future of the Expanded Choice Program and the ability of CMAC to encourage creation of additional county HIOs are in doubt. Some members of the provider community, as well as various consumer and patient advocacy groups, question the ability of these capitated programs to provide high quality care and improved access. Although often based on the self-interest of their constituencies, these objections raise legitimate questions. Nonetheless, as competition in California's health care market increases, some plan must be implemented to include low-income and medically indigent persons in the mainstream of medical care. Delays in implementing capitated programs may provide an opportunity to carefully examine the advantages and disadvantages of capitation programs for low-income and medically indigent persons.

Attempts to transform the Medi-Cal system from fee-for-service to an at-risk capitated system has been largely motivated by needs to contain costs in a highly competitive marketplace. What effect these attempts will have on the delivery of health services to California's low income population is still unknown. Children now account for a majority of enrollees in the at-risk plans and it can be argued that children's health services are already relatively inexpensive, with low ambulatory care costs and rare hospital admissions which are nearly always necessary. As a result, savings from capitation may not be the result of increased efficiency but decreased utilization generated by enrollee confusion, burdensome procedures and incomprehensible systems. Current medical information systems may be inadequate to detect such an unintended result, and may be incapable of truly determining if this reorganization of health services is both *cost-effective* and *care-effective*. Without proper safeguards for preserving those parts of the system that efficiently serve California's needy population, we may be reorganizing the health system just to throw the baby out with the bath water.

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Restless Legs Syndrome

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In a series of articles from 1944 through 1960, Ekbom brought attention to an odd condition characterized by ill-defined, unpleasant sensations in the legs that produced an irresistible urge to move, which he dubbed "restless legs."[1] Admittedly his was not a novel observation, as earlier accounts of probably the same syndrome can be found scattered in the medical literature. The 17th century neurologist Thomas Willis has generally been credited with the initial description of the restless legs syndrome. In 1880 Beard had written about a state in which "fidgetiness and nervousness, inability to keep still—a sensation that amounts to pain—is sometimes unspeakably distressing. When the legs feel this way, the sufferer must get up and walk or run."[2] Yet, perhaps because of the peculiar and subjective nature of this condition, the symptoms were very often dismissed as psychogenic in origin and the syndrome went ignored.

Even today, the restless legs syndrome frequently goes unrecognized or misinterpreted by primary care physicians, the very people who are most likely to encounter it. Indeed, it has been estimated that 5% of the population will suffer from the syndrome to some degree at some time in their lives. While this figure may be a bit inflated, new therapeutic possibilities make it worth reviewing at this time.

Clinical Features

The restless legs syndrome can be recognized by the clinical triad of unnatural feelings in the legs that only appear when the limbs are at rest and are associated with an irresistible urge to move to obtain relief. Descriptions of these queer sensations vary widely but share an uncomfortable quality. In Ekbom's series the feelings were usually of a deep-seated creeping or crawling nature located in the lower legs (although the thigh and even the upper extremities can be affected). Involvement was bilateral but not always symmetric. Others have found that adjectives such as "aching," "prickling," "tingling" and "pulling" are used just as often and that many patients are unable to differentiate whether the discomfort is superficial or deep.[3]

More distinctive than the quality or location of the sensations are their appearance only at rest and temporary amelioration by movement. While the discomfort is usually most noticeable at night, it can occur anytime a patient must sit still for a long period or is not particularly stimulated. One can often elicit a history of the syndrome being aggravated during a boring movie, reading a dull book or when watching television.

Most patients find daytime symptoms, if present, merely mildly annoying; it is at bedtime that the condition often reaches its most distressing proportions. Commonly, the paresthesias commence or worsen shortly after going to bed and interfere with falling asleep. Some patients report initially falling asleep normally, only to be awakened within hours by the discomfort. Episodes can recur during the night.

With occurrence of the sensations, there is a compulsion to move the legs for relief. Patients may stretch or massage their legs, thrash them about in bed or get up and walk around. While in mild cases the sensations gradually disappear, those more severely afflicted may be up most of the night pacing about. Insomnia can be the predominant complaint in the restless legs syndrome.

Along with their voluntary movements, patients may notice spontaneous jerking of the legs, especially at night. Questioning of bed partners often reveals that these patients kick in their sleep. Polysomnographic studies of patients show repetitive activity occurring before the onset and persisting during the first few hours of sleep.[4] These movements, manifest by dorsiflexion of the foot, along with flexion of the knee and hip, recur with a certain periodicity, such as every 20 to 40 seconds, and are termed periodic movements of sleep. These are not specific for the restless legs syndrome, having been observed in a variety of sleep disorders. Furthermore, periodic movements of sleep are not always present and may be a nonspecific consequence of chronic sleep-wake disturbances.

The syndrome can present in any age group and has allegedly been identified in persons ranging from 1 to 82 years old. Ekbom was unable to detect any age- or sex-related preponderance of the syndrome; a recent survey of 174 patients, however, found about 70% of those affected to be women, with a higher prevalence among middle-aged people.[5] The severity is highly variable, with mild cases often only discovered by specific questioning and not particularly disturbing to the patient. While the syndrome mostly occurs in isolation, it has been seen on a familial basis and in association with a number of other conditions (see below).

The course may extend over years to decades, being punctuated by periods of remission and exacerbation. There is no information on how treatment influences the natural history of the syndrome. In and of itself, the condition is considered benign.

Diagnosis

Identification of the condition is based entirely on the historical findings of unpleasant sensations in the legs appearing at rest that induce an irresistible urge to move to obtain relief. There are no characteristic physical signs nor are there any diagnostic tests.

Unfortunately, the medical literature is contaminated by reports that use the term "restless legs" in a more liberal

(Bernick C, Stern LZ: Restless legs syndrome. West J Med 1986 Aug; 145:263-265)

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sense. For example, some suggest that the syndrome can take a "pure motor" form without sensory symptoms.[6] It is certainly conceivable that partial forms of the syndrome exist, but because accurate classification is essential for meaningful study of the restless legs syndrome and its response to therapy, strict adherence to diagnostic criteria is encouraged.

Other conditions can mimic certain fragments of the syndrome. Uncomfortable sensations, often worse at night, can result from peripheral nerve disease of any cause. These paresthesias, though, do not necessarily produce an impulse to move and are not predictably relieved by movement. Moreover, the sensory and reflex examinations usually elicit abnormalities. Akathisia, that is, involuntary motor restlessness without sensory symptoms, is most commonly seen as a side effect of antipsychotic medications but may occur in encephalopathic states or dementia.[7] While these patients move and fidget constantly, they are usually able to sleep well at night in the absence of other complicating illnesses.

Etiology

As in other syndromes, a variety of disorders may be capable of producing this condition. While most cases are apparently idiopathic, a number of causes have been suggested.

The observed familial occurrence of the syndrome has led some to postulate an hereditary component. Though no systematic genetic study has been done, possibly a third or more cases have a familial incidence. An autosomal-dominant mode of inheritance has been suggested.[8]

Deficiency states have been implicated in producing the restless legs syndrome. In a series of 50 unselected neurologic outpatients with iron deficiency, nearly 25% admitted to the syndrome.[1] Similarly, a fourth of 77 unselected patients with the syndrome had low serum iron levels and in 10 iron-deficient patients with the disorder, symptoms were alleviated with iron therapy.[1] Folate deficiency has also been incriminated as an etiologic factor in both acquired and familial cases.[9] Still, most patients with restless legs have normal iron and folate values, and most patients with these deficiencies do not suffer from the syndrome.

Perhaps the highest incidence occurs in patients with uremia. Reportedly 15% to 20% of uremic patients on dialysis have the syndrome.[10] That dialysis itself is not the causative agent is shown in an earlier study that found 40% of nondialyzed patients with uremia experienced it.[11] Moreover, there appears to be no correlation between clinical evidence of peripheral neuropathy and occurrence of the syndrome.

Pregnancy has long been recognized to precipitate or exacerbate the syndrome. Indeed, its incidence in pregnant women has been said to be from 11% to 27%.[1] Symptoms tend to begin after 20 weeks and disappear soon after delivery. Some women are symptomatic only when pregnant and may experience recurrences with subsequent pregnancies. It has been proposed that a relative folate deficiency (due to increased demands during pregnancy) may contribute to the development of the syndrome.[9]

Emotional factors have been thought by some to be of importance in producing restless legs. Gorman and coworkers were impressed with the high incidence of depression and anxiety in patients with the condition, which they felt were not simply due to chronic discomfort.[3] In contradistinction, Ekbom found most of his patients to be "well-balanced persons without mental disturbances."[1]

Various other conditions have been reported in association with (usually anecdotally) or hypothesized to cause the restless legs syndrome, including cancer, prostatitis, polio, myokymia, barbiturate withdrawal, diabetes, prolonged exposure to cold, avitaminosis, cholesterol-crystal embolization, acute porphyria and following therapy with prochlorperazine or promethazine hydrochloride.[1,3,12] The significance of these relationships is dubious at best.

Pathogenesis

An intriguing and inscrutable aspect of this syndrome is its neurophysiologic basis. There is no obvious thread that ties together the heterogeneous group of disorders. It is possible that more than one pathogenetic mechanism exists; certainly many have been proposed.

Several authors have proposed a peripheral origin. Based on his impression that symptoms could be relieved by vasodilator drugs, fever and movement, Ekbom felt that there might be an accumulation of metabolites in the limbs. Similarly, some have speculated that prolonged muscle contraction may play a role.[3] Callaghan, in his review of the restless legs syndrome in cases of uremia, contended that it may result from irritation or damage to peripheral nerves. Others, though, have been unable to document electrophysiologic findings of neuropathy consistently in patients.[3]

The idea that dysfunction in the central nervous system at either the level of the spinal cord or the brain underlies the syndrome also has it advocates. Motor neuron disease and disturbances in the γ or reticular systems have all been suspected in its pathogenesis. Menninger-Lerchenthal asserted that it is due to iron deficiency in the basal ganglion.[13] Our theory is that the syndrome is due to perturbed sensory processing within the central nervous system. Many of the drugs promoted as beneficial in its treatment (see below) are known to affect various neurotransmitter systems in the brain and spinal cord involved in pain modulation and transmission. Dopaminergic projections, for example, extending from the caudal diencephalon to the dorsal horn of the spinal cord, have been identified in animals and are believed to regulate nociceptive responses.[14]

Unfortunately, there is no convincing evidence for any of these hypotheses. Thus, the pathogenesis must remain obscure until better means of unraveling this mystery are developed.

Treatment

Lacking any clear understanding of the disorder's pathophysiology, the treatment of patients with it has been empiric. A wide variety of pharmacologically diverse agents has been tried with variable responses.

Certainly in view of the reported association with iron or folate deficiency, it would make sense to check these values in all cases and correct when necessary. In fact, one may want to routinely prescribe a daily multivitamin that contains folate and iron.

Where no deficiency state is demonstrable, clinicians have a number of medications to choose from. Regrettably, the scientific data on which one might base a therapeutic decision are feeble. There have not been any controlled clinical drug trials of significant size or duration; the fluctuating nature of

the syndrome and known placebo effect make interpretation of anecdotal reports difficult.[5]

In the earlier literature, various presumed "vasodilators" were recommended. Other therapies that are said to be helpful include intravenous injections of dextran, propranolol hydrochloride at doses of 5 to 30 mg at night, methysergide maleate, clonidine and baclofen.[1,15-17] The use of carbamazepine was concluded to be more effective than a placebo in a recent short-term study.[5] Narcotic analgesics at low doses may reduce symptoms in some patients but should be avoided due to the risk of addiction.[18] Benzodiazepines have been used, with conflicting results. Some clinicians have found diazepam and chlordiazepoxide hydrochloride of value.[1,15] There have been recent reports, though, that 1 to 2 mg of clonazepam at bedtime or in split doses, alone among the benzodiazepines, suppressed the symptoms of the syndrome.[10] Administering dopaminergic agents also may be efficacious. Akpinar was able to abolish symptoms of the syndrome in five patients with the use of levodopa combined with benserazide (a dopa decarboxylase inhibitor); similar results were obtained using bromocriptine mesylate, 2.5 to 5 mg a night, in three patients.[19] Likewise, we have found the combination carbidopa/levodopa at doses from 25/100 to 25/250 mg twice a day to be beneficial in uremic patients with the restless legs syndrome.

As anyone who has treated many patients with this syndrome will attest, certain patients will be resistant to all of the previously mentioned medications. With these patients, we emphatically advise restraint before embarking on aggressive (and potentially harmful) therapy for this benign condition.

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California Birth Defects Monitoring Program

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THE California Birth Defects Monitoring Program (CBDMP) operates a large, population-based registry of children with structural congenital anomalies. The conditions being monitored (generally included within the *International Classification of Diseases, 9th Rev—Clinical Modification* codes 740-0 to 759.9) encompass disabilities due to irregularities in the development of internal and external organs and limbs, chromosomal anomalies and syndromes. The program, run by the California State Department of Health Services and the Health Officers Association of California, collects data to provide information on the prevalence of structural anomalies and to determine whether birth defects are related to suspected etiologic agents.

The program currently operates in 16 counties of California, with 165,000 births annually (Alameda, Contra Costa, San Francisco, San Mateo and Santa Clara counties for births beginning January 1, 1983, and Fresno, Merced, Monterey, Napa, Orange, Sacramento, San Joaquin, Santa Cruz, Stanislaus, Tulare and Yolo counties for births beginning January 1, 1986). On January 1, 1987, the program will be expanded to an additional 21 counties throughout California.

The program requires no reporting of congenital anomalies by either physicians or hospitals. Instead, program staff visit all hospitals and other data sources that serve children in the eligible counties. They have the legislative authority to abstract information on children and to enter this data in a confidential computer file at the State Department of Health Services. Only statistical summaries are released. Nonconfidential data will be readily available to any qualified scientist who submits a research protocol to the CBDMP.

Data from 1983 show an overall prevalence rate of severe congenital anomalies in the San Francisco Bay Area of 2.4%, and 60% of the cases were in male infants. Condition-specific rates were remarkably similar to prevalence rates in Atlanta where the Centers for Disease Control operate a similar, but much smaller, birth defects registry.

The causes of most birth defects are not known. The CBDMP represents the largest comprehensive effort to systematically collect data on children with congenital anomalies in the United States. As such, it serves as an important epidemiologic resource to help identify causes and to ease fears about suspected agents.

(Harris JA: California birth defects monitoring program [Information]. West J Med 1986 Aug; 145:265)

From the Birth Defects Monitoring Program, Epidemiological Section, Department of Health Services, Berkeley, California.

Reprint requests to John A. Harris, MD, Chief, Birth Defects Monitoring Program, Department of Health Services, 2151 Berkeley Way, Rm 515, Berkeley, CA 94704.

GENERAL REFERENCES

Grether JK: New California program monitors birth defects. J Perinatol 1985; 5:8-10

Schardein JL, Schwetz BA, Kenel MF: Species sensitivities and prediction of teratogenic potential. Environ Health Perspect 1985 Sep; 61:55-67

Smith DW, Jones KL: Recognizable Patterns of Human Malformations: Genetic, Embryologic, and Clinical Aspects, 3rd Ed. Philadelphia, WB Saunders, 1982

Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Early Detection of Lung Cancer

QUESTIONS:

In light of available methods for the diagnosis and treatment of lung cancer,

1. Is there any evidence that early diagnosis of this disease can significantly improve patient survival? If yes, what diagnostic and treatment modalities are available?

2. Is there any evidence that early detection of lung cancer's premalignant precursors can significantly improve patient survival? If yes, what screening, diagnostic and treatment modalities are available?

OPINION:

1. In the opinion of the Scientific Advisory Panels on Chest Diseases, General and Family Practice, General Surgery, Internal Medicine, Occupational Medicine, Pathology, Preventive Medicine and Public Health and Radiology, there is some evidence that certain types of lung cancer can be detected at an earlier stage than previously possible, but it has not been shown that earlier detection significantly decreases mortality from the disease. In the context of lung cancer, early diagnosis must refer to asymptomatic disease detected by screening procedures. The only diagnostic methods of potential screening value at present are chest radiography and sputum cytology. Chest radiography is acknowledged to be more sensitive than sputum cytology, but the latter, a microscopic examination of cells obtained from deep cough sputum samples, is highly specific and is more effective in detecting early squamous cell carcinoma of the lung. It has been shown that serial cytologic examinations increase resectability and average survival after surgical resection, but it has not been proved that it actually increases the length of survival.

Additional methods of value in the diagnosis of lung cancer are the history and physical examination, fiberoptic bronchoscopy, biopsy of accessible lesions (including mediastinoscopy), thoracotomy, computed tomography and magnetic resonance imaging. Sputum cytology used in conjunction with fiberoptic bronchoscopy and hematoporphyrin, a fluorescent dye, to locate very small lung tumors is considered investigational. Treatment methods of value include surgery, radiation therapy and chemotherapy, alone or in combination. Recently developed procedures such as photodynamic laser therapy and immunologic therapy are still under investigation.

The most rigorous evaluation of early detection of lung cancer is currently in progress. Sponsored by the National Cancer Institute, this project consists of three long-term, randomized, controlled clinical trials comparing radiologic and cytologic screening, alone and in combination, for the early detection of lung cancer.

Collectively, these studies (the Johns Hopkins Lung Project, the Mayo Lung Project and the Memorial Sloan-Kettering National Lung Project) recruited approximately 30,000 men, all heavy smokers 45 years of age or older.

The results of the initial screening suggest that early detection using chest radiography with sputum cytology improves five-year survival when compared with data derived from the general population. The advisory panels, however, support the conclusion of the Early Lung Cancer Detection Cooperative Study, published in 1984, which states that "these data do not yet indicate whether long survival in prevalence cases of lung cancer means a decreased mortality from the disease or simply reflects one or more of the artifacts of screening. Conclusions with regard to the impact of screening on mortality must await the outcome of long-term follow-up and incidence data now being collected in these controlled trials." Until current screening techniques are shown to reduce mortality and to be cost-effective, screening programs should be conducted only under research protocol and limited to such high-risk groups as heavy smokers and those exposed to occupational hazards known to be associated with respiratory cancer.

2. Insufficient data exist to definitively show that detection of these premalignant precursors would improve patient survival, even though it appeals to logic. Since early detection of lung cancer would seem to be a prerequisite for improved survival, randomized clinical trials on the experimental diagnostic and treatment methods previously mentioned are encouraged.

While the potential benefit of early detection programs remains to be seen, prevention of lung cancer continues to be a high priority. Intensified efforts in smoking cessation, antismoking programs and control of occupational lung cancer agents should be supported and may ultimately prove more cost-effective than early detection screening programs. At the same time, research into improved treatment methods such as photodynamic laser therapy, newer chemotherapeutic drugs and immunologic methods for regression in cellular atypia and dysplasia should be encouraged. Earlier diagnosis will be of limited value until some therapeutic technique allows definitive therapy of the lesion detected at its earliest stage.

In Memoriam

Arizona Medical Association

SAGE, CLAUDINE, Phoenix. Died June 2, 1986, aged 60. Graduate of Baylor University College of Medicine, Houston, 1950. Licensed in Arizona in 1955. Dr Sage was a member of the Arizona Medical Association.

California Medical Association

ANDERSON, NELS H., Santa Cruz. Died January 30, 1986, aged 78. Graduate of University of Minnesota Medical School, 1933. Licensed in California in 1943. Dr Anderson was a member of the Santa Cruz County Medical Society.

ARKUSH, ALBERT S., Palo Alto. Died June 21, 1986, aged 85. Graduate of the US Naval Academy at Annapolis, Md, 1920, and Stanford University School of Medicine, 1929. Licensed in California in 1929. Dr Arkush was a member of the Los Angeles County Medical Association and past president of the Bay Branch of the Los Angeles County Medical Association.

EAST, EDWARD A. Died March 27, 1986, aged 63. Graduate of the Los Angeles College of Osteopathy, 1950. Licensed in California in 1950. Dr East was a member of the San Diego County Medical Society.

FLEMING, PETER D., San Jose. Died April 8, 1986, aged 68. Graduate of Washington University School of Medicine, St Louis, 1941. Dr Fleming was a member of the Santa Clara County Medical Society.

GANS, CLARA, San Mateo. Died February 18, 1986, aged 87. Graduate of Groningen Medical College, 1921. Licensed in California in 1941. Dr Gans was a member of the Santa Clara County Medical Society.

GREEN, MARION M., Stockton. Died October 16, 1984, aged 78. Graduate of Stanford University School of Medicine, 1933. Licensed in California in 1933. Dr Green was a member of the San Joaquin County Medical Society.

HENDRICKSON, CHARLES W., Orange. Died January 12, 1986, aged 59. Graduate of Nebraska College of Medicine, 1956. Licensed in California in 1958. Dr Hendrickson was a member of the Orange County Medical Association.

HOEHN, EDWARD, Paradise. Died March 17, 1986, aged 93. Graduate of Loma Linda University School of Medicine, 1928. Licensed in California in 1928. Dr Hoehn was a member of the Napa County Medical Society.

HOLM, DONALD NATHAN, Grand Terrace. Died February 18, 1986, aged 69. Graduate of Loma Linda University School of Medicine, 1944. Licensed in California in 1947. Dr Holm was a member of the San Bernardino County Medical Society.

JOHNSON, HILDING R., Sacramento. Died January 5, 1986, aged 85. Graduate of the University of California, San Francisco, 1929. Licensed in California in 1929. Dr Johnson was a member of the Sacramento-El Dorado Medical Society.

LANGSJOEN, GEORGE E., Sacramento. Died January 2, 1986, aged 55. Graduate of the University of Kansas School of Medicine, 1955. Licensed in California in 1961. Dr Langsjoen was a member of the Sacramento-El Dorado Medical Society.

LISTON, EDWARD, Palo Alto. Died March 20, 1986, aged 86. Graduate of St Bartholomew's Hospital, London, 1922. Licensed in California in 1925. Dr Liston was a member and past president of the Santa Clara County Medical Society.

LYONS, THOMAS W., Del Cerro. Died June 3, 1986, aged 64. Graduate of St Louis University Medical School, 1947. Licensed in California in 1948. Dr Lyons was a member and past president of the San Diego County Medical Society.

MCLELLAN, ALLAN C., Hemet. Died March 23, 1986, aged 72. Graduate of California College of Medicine, Irvine. Licensed in California in 1941. Dr McLellan was a member of the Riverside County Medical Association.

MCLENNAN, CHARLES E., Portola Valley. Died March 8, 1986, aged 76. Graduate of the University of Minnesota Medical School, 1934. Licensed in California in 1947. Dr McLennan was a member of the Santa Clara County Medical Society.

MARTIN, WILLIAM R., Fort Wayne, Indiana. Died January 22, 1986, aged 69. Graduate of St Louis University School of Medicine, 1942. Licensed in California in 1946. Dr Martin was a member of the San Bernardino County Medical Society.

MASON, MARSHALL I., Walnut Creek. Died February 12, 1986, aged 83. Graduate of Stanford University Medical School, 1929. Licensed in California in 1929. Dr Mason was a member of the Santa Clara County Medical Society.

MIKKELSEN, HAROLD W., Yuba City. Died February 24, 1986, aged 89. Graduate of Loma Linda University School of Medicine, 1931. Dr Mikkelsen was a member of the Napa County Medical Society.

MOODIE, A. RUSSELL, Big Bear Lake. Died February 27, 1986, aged 99. Graduate of McGill University, Montreal, 1910. Licensed in California in 1914. Dr Moodie was a member of the Kern County Medical Society.

OLSON, G. WENDELL, Fullerton. Died February 15, 1986, aged 85. Graduate of the Washington University School of Medicine, St Louis, 1926. Licensed in California in 1927. Dr Olson was a member of the Orange County Medical Association.

PATTON, HENRY S., Orinda. Died March 2, 1986, aged 77. Graduate of Stanford University School of Medicine, 1936. Licensed in California in 1936. Dr Patton was a member of the Alameda-Contra Costa Medical Association.

❦

SAMSON, HUGH R., Santa Ana. Died February 1985, aged 63. Graduate of University of Western Ontario Faculty of Medicine, 1945. Licensed in California in 1966. Dr Samson was a member of the Orange County Medical Association.

❦

SIEGEL, ROBERT CHARLES, Hillsborough. Died February 20, 1986, aged 45. Graduate of Harvard Medical School, 1966. Licensed in California in 1967. Dr Siegel was a member of the Santa Clara County Medical Society.

❦

SMITH, J. BARRY, Avila Beach. Died April 29, 1986, aged 74. Graduate of Vanderbilt University Medical School, Nashville, Tenn, 1941. Licensed in California in 1945. Dr Smith was a past president of the San Luis Obispo County Medical Society.

❦

WOODWARD, JOHN B., Corona. Died August 21, 1985, aged 56. Graduate of University of British Columbia Faculty of Medicine, 1958. Licensed in California in 1972. Dr Woodward was a member of the Orange County Medical Association.

New Mexico Medical Society

MCMURRAY, LUCY G., Albuquerque. Died June 22, 1986, aged 78 years. Graduate of Marquette University Medical School, Milwaukee, Wis, 1943. Licensed in New Mexico in 1950. Dr McMurray was an Emeritus member of the Bernalillo County Medical Society.

❦

SMITH, MARCUS J., Santa Fe. Died May 27, 1986, aged 68. Graduate of Long Island College of Medicine, Brooklyn, NY, 1942. Licensed in New Mexico in 1948. Dr Smith was an Emeritus member of the Santa Fe County Medical Society.

VALBORG BOSMOE

1934-1986

Val Bosmoe, Editorial Assistant for *The Western Journal of Medicine,* died on June 28, 1986, at Pacific Presbyterian Medical Center, San Francisco. Ms Bosmoe joined the journal's staff in 1971. She will be deeply missed.

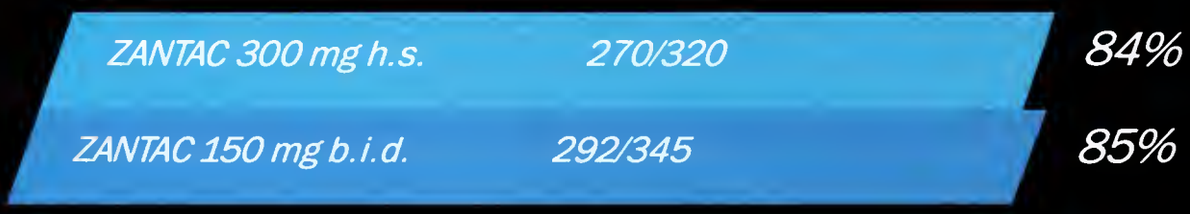
CONTROL ACID RAIN

with once-a-night h.s. therapy for active duodenal ulcers

Now, one tablet at bedtime

Controls nocturnal acid to relieve pain and heal duodenal ulcers

Heals active duodenal ulcers after 4 weeks in most patients*[1]



In well-controlled, double-blind, multicenter trials, ZANTAC 300 mg h.s. healed active duodenal ulcers in 84% of patients after 4 weeks. After 8 weeks, healing rates may be higher with ZANTAC 150 mg b.i.d. (92%) than with ZANTAC 300 mg h.s. (87%).

Relieves pain and other symptoms as effectively as ZANTAC 150 mg b.i.d.[1]

Zantac® 300

ranitidine HCl/Glaxo 300 mg tablets

Once-daily dosing may enhance compliance in patients for whom dosing convenience is important

Side-effects profile comparable to ZANTAC 150 mg b.i.d.[1-3]

Headache—sometimes severe—has been reported. Rare effects on the CNS, cardiovascular, GI, hepatic, and integumental systems have been observed, as well as rare cases of hypersensitivity reactions. See ADVERSE REACTIONS section of Brief Summary of Product Information before prescribing.

No significant interference with the hepatic cytochrome P-450 enzyme system at recommended doses

ZANTAC 300 mg h.s. had no significant drug interactions with theophylline or warfarin. The bioavailability of certain medications whose absorption is dependent on a low gastric pH may be altered when ZANTAC or other medications which decrease gastric acidity are administered.

It is not known exactly how much acid inhibition is needed to heal ulcers.

Glaxo / ROCHE

See next page for references and Brief Summary of Product Information.

IN ACTIVE DUODENAL ULCERS

Once-a-night h.s. therapy controls acid rain

Zantac® 300
ranitidine HCl/Glaxo 300 mg tablets

References: 1. Data available on request, Glaxo Inc. 2. Ireland A, Colin-Jones DG, Gear P, et al: Ranitidine 150 mg twice daily vs 300 mg nightly in treatment of duodenal ulcers. *Lancet* 1984;2:274-275. 3. Colin-Jones DG, Ireland A, Gear P, et al: Reducing overnight secretion of acid to heal duodenal ulcers. *Am J Med* 1984; 77 (suppl 5B):116-122.

ZANTAC® 150 Tablets
(ranitidine hydrochloride)
ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY OF PROOUCT INFORMATION

INOICATIONS ANO USAGE: ZANTAC® is indicated in:
1. Short-term treatment of active duodenal ulcer. Most patients heal within four weeks. Studies available to date have not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than eight weeks.
2. Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers. No placebo-controlled comparative studies have been carried out for periods of longer than one year.
3. The treatment of pathological hypersecretory conditions (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of active, benign gastric ulcer. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated. Studies available to date have not assessed the safety of ranitidine in uncomplicated, benign gastric ulcer for periods of more than six weeks.
5. Treatment of gastroesophageal reflux disease. Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **OOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Orug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (6
82 years of age) were no different from those in younger age gro
The incidence rates for adverse events and laboratory abnormali
were also not different from those seen in other age groups.

AOVERSE REACTIONS: The following have been reported as event
clinical trials or in the routine management of patients treated
oral ZANTAC®. The relationship to ZANTAC therapy has b
unclear in many cases. Headache, sometimes severe, seems t
related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolen
insomnia, and vertigo. Rare cases of reversible mental confus
agitation, depression, and hallucinations have been reported,
dominantly in severely ill elderly patients.

Cardiovascular: Rare reports of tachycardia, bradycardia, and
mature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting,
abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased t
least twice the pretreatment levels in 6 of 12 subjects receiv
100 mg qid IV for seven days, and in 4 of 24 subjects receiv
50 mg qid IV for five days. With oral administration there have b
occasional reports of reversible hepatitis, hepatocellular or hepa
canalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Rare reports of reversible leukopenia, granuloc
penia, thrombocytopenia, and pancytopenia.

Endocrine: Controlled studies in animals and man have shown
stimulation of any pituitary hormone by ZANTAC and no antianc
genic activity, and cimetidine-induced gynecomastia and im
tence in hypersecretory patients have resolved when ZANTAC
been substituted. However, occasional cases of gynecomast
impotence, and loss of libido have been reported in male patie
receiving ZANTAC, but the incidence did not differ from that in
general population.

Integumental: Rash, including rare cases suggestive of mild e
thema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospas
fever, rash, eosinophilia) and small increases in serum creatinin

OVERDOSAGE: There is no experience to date with deliberate ov
dosage. The usual measures to remove unabsorbed material fr
the gastrointestinal tract, clinical monitoring, and supportive th
apy should be employed.

Studies in dogs receiving doses of ZANTAC® in excess
225 mg/kg/day have shown muscular tremors, vomiting, and ra
respiration. Single oral doses of 1,000 mg/kg in mice and rats w
not lethal. Intravenous LD_{50} values in rat and mouse were 83 a
77 mg/kg, respectively.

**OOSAGE ANO AOMINISTRATION: Dosage Adjustment for Patients w
Impaired Renal Function:** On the basis of experience with a gro
of subjects with severely impaired renal function treated w
ZANTAC®, the recommended dosage in patients with a creatin
clearance less than 50 ml/min is 150 mg every 24 hours. Shou
the patient's condition require, the frequency of dosing may
increased to every 12 hours or even further with caution. Hemo
alysis reduces the level of circulating ranitidine. Ideally, the dosa
schedule should be adjusted so that the timing of a scheduled do
coincides with the end of hemodialysis.

HOW SUPPLIEO: ZANTAC® 150 Tablets (ranitidine hydrochlor
equivalent to 150 mg of ranitidine) are white tablets embossed w
"ZANTAC 150" on one side and "Glaxo" on the other. They a
available in bottles of 60 tablets (NDC 0173-0344-42) and u
dose packs of 100 tablets (NDC 0173-0344-47).

ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent
300 mg of ranitidine) are yellow, capsule-shaped tablets embosse
with "ZANTAC 300" on one side and "Glaxo" on the other. They a
available in bottles of 30 (NDC 0173-0393-40) and unit do
packs of 100 tablets (NDC 0173-0393-47).

**Store between 15° and 30°C (59° and 86°F) in a dry place. Protect fr
light. Replace cap securely after each opening.**

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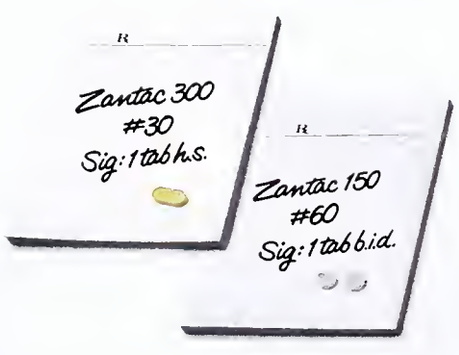
Glaxo
Glaxo Inc.
Research Triangle Park, NC 27709

Now...two effective regimens to treat active duodenal ulcers



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(Continued from Page 178)

tact: Antonio De La Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

December 4-7—**2nd Annual Fracture Management Symposium.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Thursday-Sunday. 18 hrs. Fee: $475. Contact: UCD.

December 7-19—**Temporal Bone Surgical Dissection and Cochlear Implant.** House Ear Institute. Sunday-Friday. 100 hrs. Fee: $1,700. Contact: Antonio De La Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

January 19-21—**American Society for Surgery of the Hand's 1st Winter Meeting.** Pacific Medical Center, San Francisco. Monday-Wednesday. Contact: American Society for Surgery of the Hand, 3025 S Parker Rd, Ste 65, Aurora, CO 80014.

January 19-23—**10th Annual Postgraduate Assembly in Surgery.** UCSD at US Grant Hotel, San Diego. Monday-Friday. 30 hrs. Contact: UCSD.

OF INTEREST TO ALL PHYSICIANS

August 16-27—**Hawaii Refresher Course.** USC at Honolulu/Maui. Saturday-Wednesday. 37 hrs. Fee: $535. Contact: USC.

August 21-22—**General Medicine for Practicing Physicians Update.** Northern Inyo Hospital at Bishop. Thursday-Friday. 10 hrs. Fee: $75. Contact: Mrs Barbara Parcher, Northern Inyo Hospital-Medical Education Bldg, 150 Pioneer Lane, Bishop, CA 93514.

September 5—**3rd Symposium in Geriatric Medicine—Use It or Lose It: Exercise and Aging.** STAN at STAN. Friday. Contact: STAN.

September 11-13—**What the Clinician Should Know about the Treatment of Chemical Dependencies.** California Society for the Treatment of Alcohol and other Drug Dependencies at Marriott Hotel, Los Angeles Airport. Thursday-Saturday. 15-18 hrs. Fee: $350-400. Contact: Sandy Swift, 3803 Broadway, Ste 2, Oakland 94611. (415) 428-9091.

September 17-19—**Spine Update: 1986.** UCSF at San Francisco Hyatt Regency. Wednesday-Friday. Contact: UCSF.

September 18-20—**Understanding Common Adolescent Problems: A Conference on the Family.** UCSF. Thursday-Saturday. 16 hrs. Fee: $225. Contact: UCSF.

September 19-20—**Developing Services for Comprehensive AIDS Care: A Workshop.** UCSF at St Francis Hotel, San Francisco. Friday-Saturday. 11 hrs. Fee: $225. Contact: UCSF.

September 19-20—**Progress in Impotence: Diagnosis and Therapy.** UCSD at Hotel Inter-Continental, San Diego. Friday-Saturday. 13 hrs. Fee: $295. Contact: UCSD.

September 18-21—**California Conference on Applied Clinical Geriatrics.** UCD at Yountville Veterans' Home, Napa Valley. Thursday-Sunday. Contact: UCD.

September 18-21—**Making a Difference: A Workshop for International Health Volunteers.** Plastic Surgery Foundation of San Diego at San Diego Hilton Beach and Tennis Resort. Thursday-Sunday. Fee: $125. Contact: Plastic Surgery Foundation of San Diego, PO Box 33387, San Diego 92103. (619) 692-9115.

September 24-26—**Primary Care Medicine: Principles and Practice.** UCSF at Golden Gateway Holiday Inn, San Francisco. Wednesday-Friday. 19.5 hrs. Fee: $350. Contact: UCSF.

September 25-28—**Skills Update—Intensive Workshop in Sexuality.** American Association of Sex Educators, Counselors and Therapists at Sir Francis Drake Hotel, San Francisco. Thursday-Sunday. 18 hrs. Fee: $150-175. Contact: William Stull, AASECT Conference, 2333 N 3rd St, Phoenix, AZ 85004. (602) 252-2706.

September 26-27—**Samuel Merritt Hospital 41st Annual Seminar: Highlights of New Diagnostic and Therapeutic Approaches in Medicine.** Samuel Merritt Hospital, Oakland. Friday-Saturday. Fee: $50. Contact: Samuel Merritt Hospital, Medical Staff Office, Hawthorne Ave and Webster St, Oakland 94609. (415) 420-6065.

October 4-11—**Effective Diagnosis and Treatment of Infectious Diseases: California Wine Country Bicycling Tour.** University of Arizona at Guerneville. One Week. 24 hrs. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

October 15—**Alcohol and Drug Dependency.** Kaiser Permanente Medical Group at Long Beach Hyatt Hotel. Wednesday. 6 hrs. Fee: $100. Contact: Judy Harrison, Dept of Clinical Services, Southern California Permanente Medical Group, 393 E Walnut St, Pasadena 91188.

October 17-19—**Practical Gastroenterology and Flexible Sigmoidoscopy for the Practicing Physician.** UCSD and Continuing Medical Education Associates at Vacation Village Resort, San Diego. Friday-Sunday. 20 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

October 19-21—**Alcohol Related Birth Defects.** UCSD at Kona Kai Resort, San Diego. Sunday-Tuesday. 13.5 hrs. Contact: UCSD.

October 22—**Update on Diabetes.** Hospital of Good Samaritan, Los Angeles at Moseley-Salvatori Conference Center, Los Angeles. Wednesday. 7 hrs. Contact: Dolores Gay, 616 S Witmer St, Los Angeles 90017. (213) 977-2352.

October 23-25—**International Conference.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. Contact: UCSF.

October 23-25—**Postgraduate Institute for Monterey Counties.** CMA at Sheraton, Monterey. Thursday-Saturday. Contact: Janice Rigney, CMA.

October 31—**Managing and Controlling Asbestos Contamination/Exposure.** USC. Friday. Fee: $150. Contact: USC.

November 3-6—**Intervention Workshop.** Scripps Memorial Hospital. Monday-Thursday. 26.5 hrs. Fee: $250. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

November 5—**Common Musculo-Skeletal Problems.** Veterans Administration Medical Center, Sepulveda. Wednesday. 5 hrs. Contact: Arun J. Mehta, MD, Rehabilitation Medicine Service (117), VAMC, Sepulveda 91343. (818) 891-2473.

November 7-8—**Medical Advances in the 80s: A Multi-Specialty Update—UCD 20th Anniversary.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. Contact: UCD.

November 8-10—**State of the Art Urology—Live Television Coverage of Surgery.** UCLA at Miramar Sheraton Hotel, Santa Monica. Saturday-Monday. 21 hrs. Fee: $400. Contact: UCLA.

November 10-14—**Intensive Care.** STAN at STAN. Monday-Friday. Contact: STAN.

November 14—**22nd Annual California Medical Center Staff Seminar: New Concepts in Medicine.** Los Angeles. Friday. 6 hrs. Fee: $50. Contact: California Medical Center, Kenneth L. Senter, MD, 1414 S Hope St, Los Angeles 90015. (213) 742-5750.

November 14-16—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital and Continuing Medical Education Associates at Hotel Del Coronado, San Diego. Friday-Sunday. 18 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

November 21—**Orthopedic Symposium.** Kaiser Permanente Medical Group at Marina Beach Hotel, Marina Del Rey. Friday. 7 hrs. Fee: $100. Contact: Judy Harrison, Dept of Clinical Services, Southern California Permanente Medical Group, 393 E Walnut St, Pasadena 91188. (818) 405-5000.

November 22—**Alzheimer's Disease—An Overview.** UCI at UCI. Saturday. 5.5 hrs. Contact: UCI.

November 22-29—**Stress Management: Hawaiian Islands Cruise Adventure.** University of Arizona. One Week. 24 hrs. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

December 11-12—**AIDS and the Nervous System.** UCSF at St Francis Hotel, San Francisco. Thursday-Friday. 10 hrs. Contact: UCSF.

January 12-16—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD at San Diego Hilton Hotel. Monday-Friday. 32 hrs. Fee: $325-400. Contact: UCSD.

January 16-17—**Cardiology for the Non-Cardiologist.** UCI at Long Beach. Friday-Saturday. Contact: UCI.

January 19-21—**Pediatrics for the Primary Care Physician.** UCSD at Vacation Village Resort, San Diego. Monday-Wednesday. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 23-25—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** Continuing Medical Education Associates at San Diego. Friday-Sunday. 20 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

January 26-28—**Recent Advances in Geriatric Medicine—1987.** UCSD at Holiday Inn Embarcadero, San Diego. Monday-Wednesday. 18 hrs. Contact: UCSD.

January 28-30—**Neurology for Non-Neurologists.** UCSD at Holiday Inn Embarcadero, San Diego. Wednesday-Friday. 21 hrs. Fee: $375. Contact: UCSD.

January 30-February 1—**Primary Care Update—1987: A Practical Approach.** Scripps Clinic and Research Foundation at Vacation Village Resort, San Diego. Friday-Sunday. Fee: $200. Contact: Bonny Mower, Dept of Academic Affairs, PO Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

(Continued on Page 276)

ACCREDITED SEMINARS on the CONSERVATIVE MANAGEMENT of LOW BACK PAIN

A Clear Direction for Treatment in an Innovative Educational Format

Leading orthopaedic surgeons, neurosurgeons and medical specialists who are experts on the lumbar spine present a comprehensive protocol especially for the primary care physician. The protocol is designed to eliminate frustrating and time-consuming trial and error processes. The seminar program includes:

- incisive diagnosis techniques and helpful exam forms
- the most effective modalities of treatment
- an algorithm for determining patient progress by evaluating response within a time frame
- discussion of the latest surgical techniques and chemonucleolysis
- patient education for injury prevention
- an information manual

Seminars are accredited by the American Medical Association and the American Academy of Family Physicians.

October 24-25, 1986 — Salt Lake City, UT

Keynote Speakers:
David Selby, M.D., Arthur White, M.D., Jeffrey Saal, M.D.

Sponsored by Intermountain Health Care, Inc., Cottonwood Hospital Back Institute and Camp International, Inc.

For more information, contact:

CAMP INTERNATIONAL, INC.
Isabelle S. Firestone
Director of Medical Informatics
P.O. Box 89
Jackson, MI 49204
(517) 787-1600

California Medical Association
presents

Medical Staff Leadership Conferences

An invaluable opportunity for new and incumbent medical staff leaders to explore legal and organizational issues facing today's medical staff.

❑ **Saturday, September 13, Sacramento**
Sacramento-El Dorado Medical Society

❑ **Saturday, November 8, Palm Springs**
Annenberg Center for Health Sciences of the Eisenhower Medical Center

Agenda are identical for both programs, except for luncheon speaker

- **The Medical Staff Disciplinary Process: Investigation, Fair Hearing and Appeal.**
- **Credentialing of Allied Health Practitioners.**
- **Luncheon Speaker:** *Sacramento* – Assemblyman Phil Isenberg (D)

  Palm Springs – State Senator Robert B. Presley (D)
- **Peer Review Organization (CMRI) Update: The Sanction Process.**
- **Utilization Review: Appropriateness of Patient Care Documentation.**
- **Exclusive Contracts and the Medical Staff.**

For further information and telephone registration, please contact:

Medical Staff Liaison
Department of Medical Staff Affairs
California Medical Association
Post Office Box 7690
San Francisco, CA 94120-7690
☎ (415) 863-5522

Cosponsored by CMA's Hospital Medical Staff Section and Committee on Medical Staff Affairs

(Continued from Page 274)

September 11-13—**Concepts and Controversies in Perinatal Care.** Albuquerque. Thursday-Saturday. Clarion Four Seasons. AMA Cat. 1. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

September 20—**NM Physicians Mutual Liability Insurance Company Annual Loss Control Seminar.** Albuquerque. Saturday. Convention Center. Contact: K.D. Dickson, NMPMLIC, 303 San Mateo NE, Albuquerque 87108. (505) 262-1941.

September 26—**John N. Wilson, MD, Lectureship in Cardiovascular Disease.** Albuquerque. Friday. Marriott Hotel. 6 hrs. Cat. 1. Contact: Ann Nelson, Presbyterian Heart Institute, PO Box 26666, Albuquerque 87125. (505) 841-1438.

October 10-11—**Second Annual Balloon Fiesta Lung Disease Conference.** Albuquerque. Friday-Saturday. Contact: NM Chapter, American Thoracic Society, 216 Truman NE, Albuquerque 87108. (505) 265-0732.

October 10-12—**New Mexico Pediatric Association—Behavioral Disorders, Adolescent Adjustment Reaction, Sexual Abuse of Pre-adolescents.** Friday-Sunday. AMA Cat. 1. Contact: Charles Anderson, MD, PO Box 6132, Taos 87571. (505) 758-8651.

November 7-8—**New Mexico Medical Society Interim Meeting.** Las Cruces. Friday-Saturday. Holiday Inn de Las Cruces. Contact: New Mexico Medical Society, 303 San Mateo NE, Albuquerque 87108. (505) 266-7868

December 4-6—**Annual Meeting—New Mexico Chapter, American College of Physicians/New Mexico Society of Internal Medicine.** Thursday-Saturday. AMA Cat. 1. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave, Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 W Harvard Ave, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 W Harvard Ave, Roseburg 97470. (503) 673-6641.

Emanuel Hospital, 2801 N Gantenbein St, Portland 97227:

Every Friday, 12:15 p.m. to 1:00 p.m. **Medical Grand Rounds.** Contact: Philippa McClure, Emanuel Hospital, 2801 N Gantenbein St, Portland 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Ave, Portland 97210:

Every Tuesday, 12:00 noon to 1:00 p.m. **Medicine Grand Rounds.** Neurological Sciences Buildings, First Floor Auditorium. Contact: Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Ave, Portland 97201. (503) 229-7454.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder St, Eugene 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene 97440.

Salem Hospital, 665 Winter St SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St SE, Salem 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St SE, Salem 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St Vincent Hospital & Medical Center, 9205 SW Barnes Rd, Portland 97225. (503) 297-4411, Ext 2230.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

ATTENTION

OB-GYN FAMILY PRACTICE AND GENERAL PRACTICE PHYSICIANS!
ARE YOU PAYING TOO MUCH FOR YOUR MALPRACTICE INSURANCE?

Now may be the appropriate time to lower your malpractice risks by incorporating bariatric medicine into your medical practice. Bariatric medicine is a low risk malpractice specialty and deals with the medical management of obesity by physicians who have a special interest in treating overweight patients. The American Society of Bariatric Physicians (ASBP) is a Category I CME Provider that can help you learn to treat your obese patients. Physicians are needed nationwide to provide care and meet the demand for ASBP's physician referral service. New ASBP members are especially needed in the states of Oregon, Idaho, Utah, Montana, Wyoming, New Mexico, North Dakota, South Dakota, Nebraska, Massachusetts, and Vermont. We can help you educationally and in the practical business aspects of establishing a bariatric practice through our Preceptorship Program. It is estimated 30% of Americans are overweight and spend $10 billion a year trying to lose weight. However, physicians are treating less than 1/10 of 1% of their own obese patients. Now is the time for you to act and begin providing your patients care. Come to beautiful Colorado and learn from expert clinicians, educators, and researchers the proper treatment of your obese patients.

Please send information on:

☐ 36th Annual Obesity and Associated Conditions Symposium "Exploring New Heights in Bariatric Medicine" in beautiful Colorado Springs, Colorado, September 17-20, 1986

☐ Membership in the American Society of Bariatric Physicians. As a member, you receive direct benefits from patient referrals through our nationwide referral service.

☐ All future educational programs.

NAME _____

ADDRESS _____

CITY _____ STATE _____ ZIP _____

COME TO COLORADO SPRINGS—SEPTEMBER 17-20,1986

American Society of Bariatric Physicians
7430 East Caley Avenue, Suite 210
Englewood, Colorado 80111 303-779-4833

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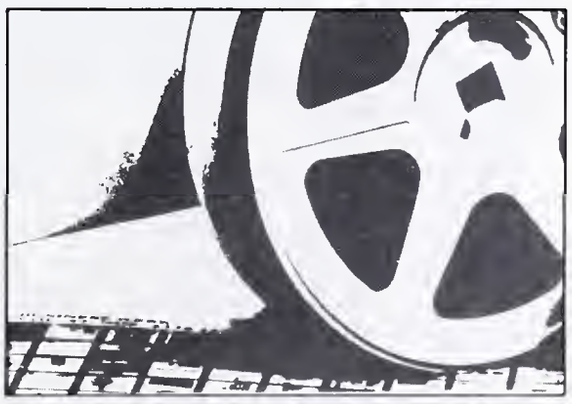

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Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept of Psychiatry, Oregon Health Sciences University, Portland 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept of Medicine, Oregon Health Sciences University, Portland 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland 97201. (503) 225-7590.

EMERGENCY MEDICINE

October 23-24—**Pediatric Advanced Life Support.** Portland. Thursday-Friday. Red Lion Motor Inn/ Portland Center. Contact: OHSU-CME.

November 14-15—**Symposium on Critical Care Medicine.** Portland. Thursday-Friday. Red Lion Motor Inn/Jantzen Beach. Contact: OHSU-CME.

FAMILY PRACTICE

October 23-25—**Pacific Northwest Review of Obstetrics and Gynecology.** See below.

OBSTETRICS AND GYNECOLOGY

October 23-25— **Pacific Northwest Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion Motor Inn/Jantzen Beach. Contact: OHSU-CME.

PEDIATRICS

October 23-24—**Pediatric Advanced Life Support.** Portland. Thursday-Friday. Red Lion Motor Inn/ Portland Center. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

September 5-6—**The Ashland Conference: Endocrinology.** Ashland. Friday-Saturday. Ashland Hills Inn. Contact: OHSU-CME.

October 10-12—**The Salishan Conference: Cardiology.** Gleneden Beach. Friday-Sunday. Salishan Lodge. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

July 13-18—**Summer Update in Clinical Microbiology and Immunology** (Sponsor: University of Utah). Sunday-Friday. Jackson Hole, Wyoming. 23 hrs. Contact: John Matsen, MD, (801) 581-7480.

(Continued on Page 280)

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

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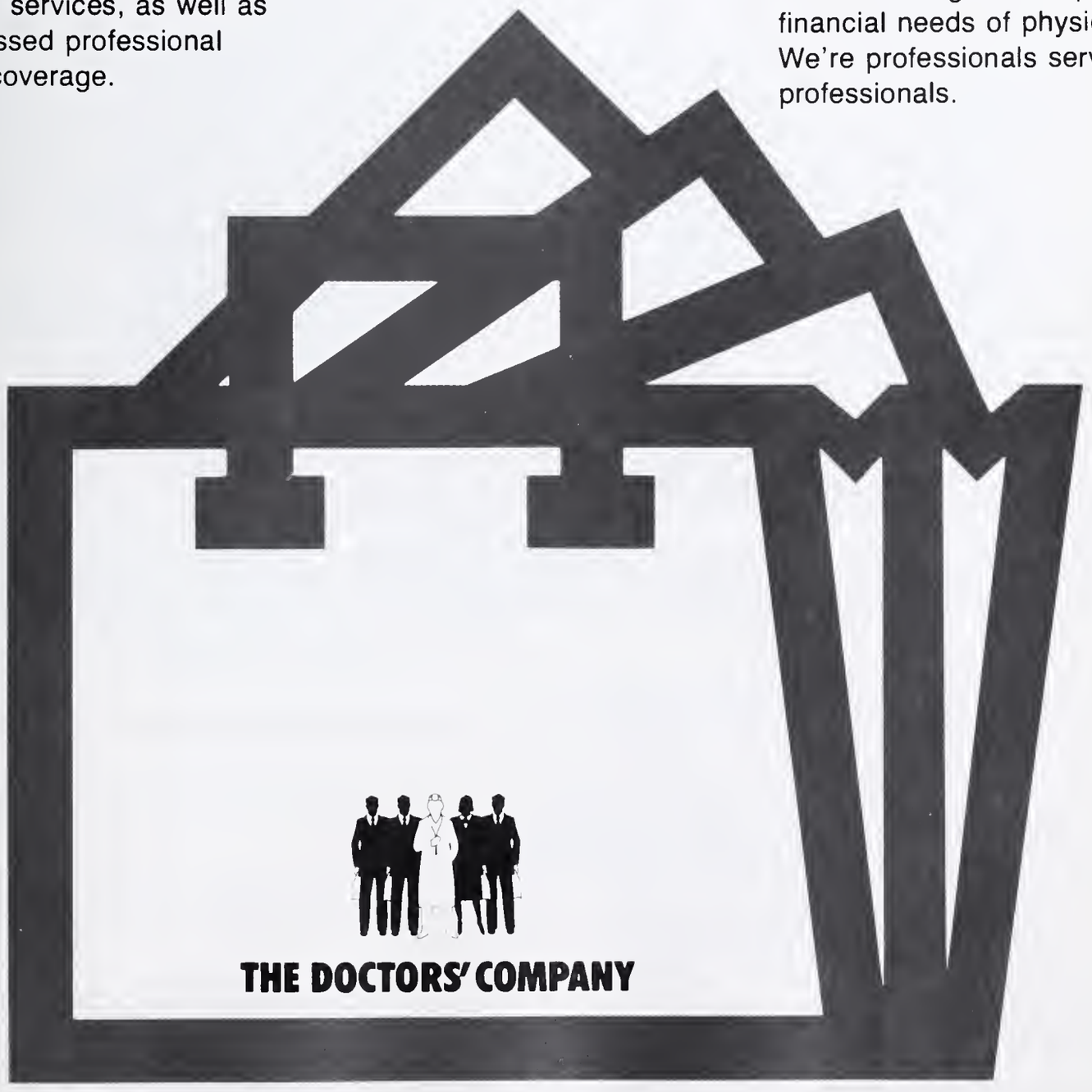


01 WILSHIRE BOULEVARD, SANTA MONICA, CA 90401 (213) 451-3011 (800) 352-7271 (CALIFORNIA) (800) 421-2368 (OUTSIDE CALIFORNIA)

(Continued from Page 278)

July 25-26—**Diabetes Update** (Sponsor: UUMC). Friday-Saturday. Utah State University, Logan. 8 hrs. Contact: Chuck Hand, (801) 363-3024.

August 25-28—**Practices and Procedures in Asbestos Abatement** (Sponsor: UUMC). Monday-Thursday. University of Utah Medical Center. Contact: Connie Crandall, Univ of Utah, Bldg 512, Salt Lake City 84112. (801) 581-5710.

September 4-5—**Postgraduate Laser Program—GI.** (Sponsor: UUMC). Thursday-Friday. University of Utah Medical Center, Salt Lake City. 10 hrs. Contact: John Dixon, MD, (801) 581-2256.

September 10-12—**Utah State Medical Association Annual Meeting.** Wednesday-Friday. Yarrow Holiday Inn, Park City. Contact: USMA, 540 E Fifth South, Salt Lake City 84102. (801) 335-7477.

September 12-13—**Attention Deficit Disorder in Children and Adults** (Sponsor: UUMC). Friday-Saturday. Snowbird Resort. 6 hrs. Contact: Paul Wender, MD, (801) 581-8664.

September 19—**American College of Physicians Regional Scientific Meeting** (Sponsor: ACP). Friday. Sheraton Hotel, Salt Lake City. Contact: C. DuWayne Schmidt, MD, 333 South 900 East, Salt Lake City 84102. (801) 535-8149.

September 19-20—**Postgraduate Laser Program—GYN** (Sponsor: UUMC). Friday-Saturday. University of Utah Medical Center, Salt Lake City. 10 hrs. Contact: John Dixon, MD, (801) 581-2256.

September 25-26—**Postgraduate Laser Program—Urology** (Sponsor: UUMC). Thursday-Friday. University of Utah Medical Center, Salt Lake City. 10 hrs. Contact: John Dixon, MD, (801) 581-2256.

October 6-8—**Occupational Low Back Pain** (Sponsor: UUMC). Monday-Wednesday. Snowbird Resort. 15 hrs. Contact: Connie Crandall, (801) 581-3841.

October 31-November 1—**Stress, Emotion and Heart Disease** (Sponsor: UUMC). Friday-Saturday. Marriott Hotel, Salt Lake City. 15 hrs. Contact: Hilmon Castle, MD, (801) 581-8664.

November 7-8—**Advanced Trauma Life Support** (Sponsor: UUMC). Friday-Saturday. Quality Inn, Salt Lake City. 16 hrs. Contact: Carla Holmes, (801) 533-6608.

November 20-21—**Postgraduate Laser Program—GI.** (Sponsor: UUMC). Thursday-Friday. University of Utah Medical Center, Salt Lake City. 10 hrs. Contact: John Dixon, MD, (801) 581-2256.

January 5-14—**Hip and Knee Bioskills Workshop** (Sponsor: UUMC). 10 days. Snowbird Resort. 15 hrs. Contact: Aaron Hoffman, MD, (801) 581-8664.

January 20-22—**Pulmonary Function Testing** (Sponsor: UUMC). Tuesday-Thursday. RMCOEH, University of Utah Medical Center. 18 hrs. Contact: Connie Crandall, (801) 581-8719.

February 1-6—**Diagnostic Imaging/Interventional Radiology** (Sponsor: UUMC). Sunday-Friday. Snowbird Resort. 20 hrs. Contact: Judy Gallegos, (801) 581-8188.

February 10-13—**Family Practice Refresher Course** (Sponsor: UUMC). Tuesday-Friday. Salt Lake City, Westin Hotel Utah. 28 hrs. Contact: Denise Denton, (801) 581-5224.

February 11-14—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wednesday-Saturday. Salt Lake City. 17 hrs. Contact: (801) 521-1221.

February 12-14—**Rigid Fixation Techniques/Craniomaxillofacial Surgery** (Sponsor: UUMC). Thursday-Saturday. Snowbird Resort. 20 hrs. Contact: Louis Morales, MD, (801) 581-8664.

February 14-21—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). One week. Park City Resort. 25 hrs. Contact: John Matsen, MD, (801) 581-7480.

February 16-20—**Surgical Pathology Workshops** (Sponsor: UUMC). Monday-Friday. Park City Resort. 20 hrs. Contact: Tom Colby, MD, (801) 581-7480.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

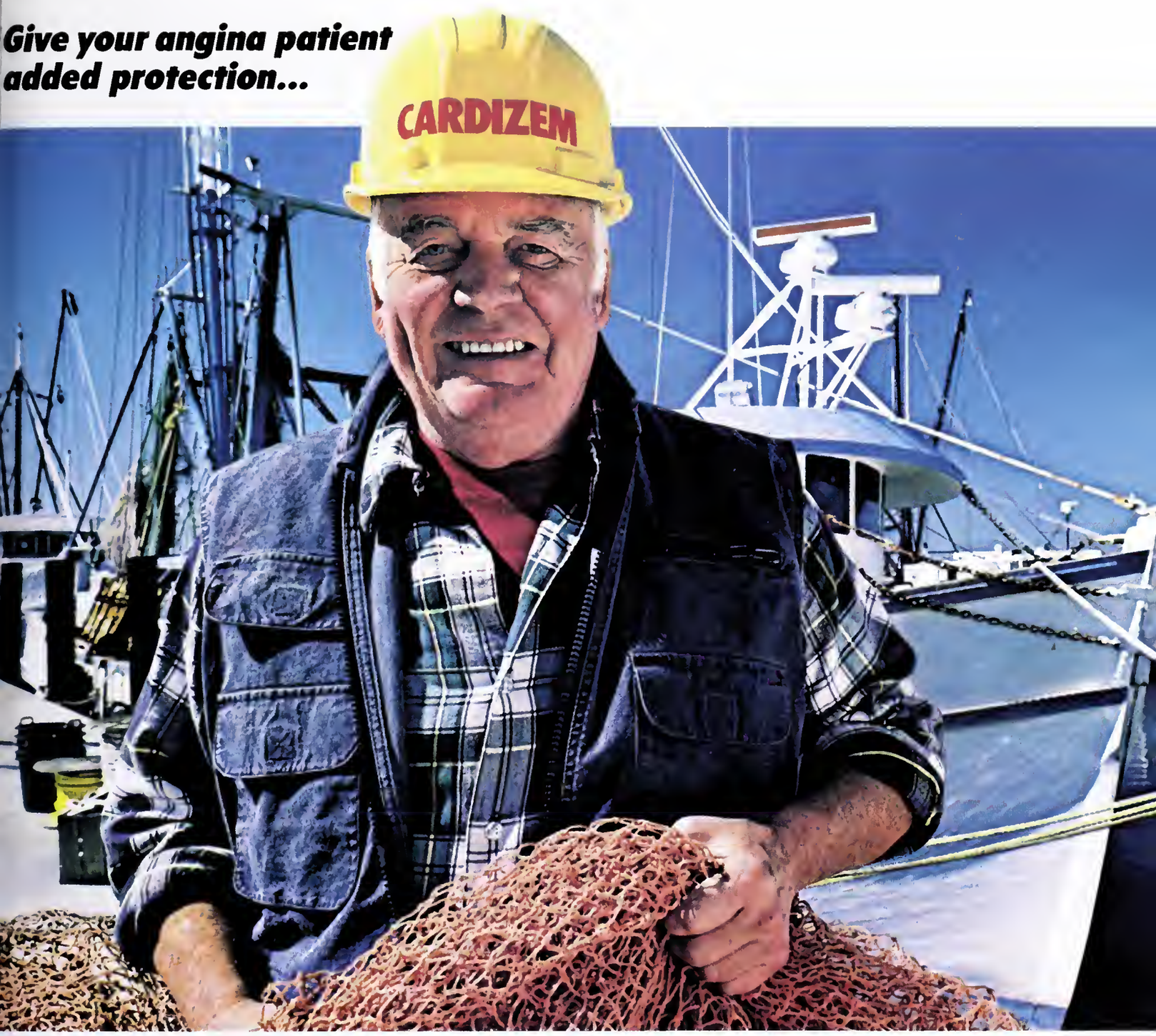
August 14-15—**Maxillofacial Trauma.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

August 21-22—**Surviving the Elements.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

August 29—**Flexible Sigmoidoscopy in Colorectal Disease.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

(Continued on Page 283)

Give your angina patient added protection...



CARDIZEM®: FEWER SIDE EFFECTS

diltiazem HCl/Marion

- ***The lowest incidence of side effects among the calcium channel blockers*** [1-6]
- ***A safe choice for angina patients with coexisting hypertension, asthma, COPD, or PVD*** [4,7]
- ***Proven efficacy when used alone in angina*** [3]
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****See Warnings and Precautions.***

Please see brief summary of prescribing information on the next page.

CARDIZEM® FEWER SIDE EFFECTS IN ANTIANGINAL THERAPY

diltiazem HCl/Marion 60 mg tid or qid

Brief Summary
Professional Use Information
CARDIZEM®
(diltiazem HCl) 30 mg and 60 mg Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. ***Cardiac Conduction.*** *CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.*
2. ***Congestive Heart Failure.*** *Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using the drug in such patients.*
3. ***Hypotension.*** *Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.*
4. ***Acute Hepatic Injury.*** *In rare instances, significant elevations in enzymes such as alkaline phosphatase, CPK, LDH, SGOT, SGPT, and other symptoms consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)*

PRECAUTIONS

General. *CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.*

Drug Interaction. *Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)*

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. *A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.*

Pregnancy. *Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.*

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. *Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.*

Pediatric Use. *Safety and effectiveness in children have not been established.*

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	*Angina, arrhythmia, AV block (first degree), AV block (second or third degree — see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.*
Nervous System:	*Amnesia, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.*
Gastrointestinal:	*Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.*
Dermatologic:	*Petechiae, pruritus, photosensitivity, urticaria.*
Other:	*Amblyopia, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.*

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established. *Issued 11/85*

See complete Professional Use Information before prescribing.

References: ***1.*** *Frishman WH, Charlap S, Goldberger J, et al: Comparison of diltiazem and nifedipine for both angina pectoris and systemic hypertension. Am J Cardiol 1985;56:41H-46H.* ***2.*** *Weiner DA, McCabe CH, Cutler SS, et al: The efficacy and safety of high-dose verapamil and diltiazem in the long-term treatment of stable exertional angina. Clin Cardiol 1985;7:648-653.* ***3.*** *Pepine CJ, Feldman RL, Hill JA, et al: Clinical outcome after treatment of rest angina with calcium blockers: Comparative experience during the initial year of therapy with diltiazem, nitedipine, and verapamil. Am Heart J 1983;106(6):1341-1347.* ***4.*** *Cahn PF, Brounwold E: Chronic ischemic heart disease, in Brounwold E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39.* ***5.*** *McCall D, Walsh RA, Frohlich ED, et al: Calcium entry blocking drugs: Mechanisms of action, experimental studies and clinical uses. Curr Probl Cardiol 1985;10(8):6-80.* ***6.*** *Chaffman M, Brogden RN: Diltiazem. A review of its pharmacological properties and therapeutic efficacy. Drugs 1985;29:387-454.* ***7.*** *Schroeder JS: Calcium and beta blockers in ischemic heart disease: When to use which. Mod Med 1982;50 (Sept):94-116.* ***8.*** *Shapira W: Calcium channel blockers: Actions on the heart and uses in ischemic heart disease. Consultant 1984;24(Dec):150-159.* ***9.*** *Johnston DL, Lesoway R, Humen DP, et al: Clinical and hemodynamic evaluation of propranalol in combination with verapamil, nifedipine and diltiazem in exertional angina pectoris: A placebo-controlled, double-blind, randomized, crossover study. Am J Cardiol 1985;55:680-687.*

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(Continued from Page 280)

September 4-5—**Plastic Repair and Wound Management.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

September 5-6—**Head and Neck Surgery Update.** With the Cleveland Clinic and the Scripps Clinic. Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

September 10-12—**Occupational Hazards to Health Care Workers.** Seattle. Wednesday-Friday. NW Center for Occupational Health and Safety. Contact: U/W.

September 8-12—**Advances in Family Practice.** Seattle. Monday-Friday. U/W Health Sciences Building. Contact: U/W.

September 11-13—**Physician Assistants—1986 Fall Meeting.** Spokane. Thursday-Saturday. Inn at the Park. Contact: WSMA.

September 13-20—**Effective Management of Common Sports Injuries.** San Juan Islands Bicycle Tour. One week. Epic Medical Expeditions. Contact: U/AZ.

September 18-19—**Brain Injury.** Seattle. Thursday-Friday. Contact: U/W.

September 18-21—**Washington State Medical Association** Annual Meeting. Spokane. Thursday-Sunday. Inn at the Park. Contact: WSMA.

September 25-27—**American Society of Internal Medicine Annual Meeting: Reimbursement, Review & Retooling: On the Road Again.** Seattle. Thursday-Saturday. Contact: ASIM, (202) 289-1700.

September 27—**Arthur A Ward Symposium.** Seattle. Saturday. U/W Health Sciences Building. Contact: U/W.

October 3—**Topics in Pulmonary Medicine: Pulmonary Infection.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

October 15—**Legal Aspects of Occupational Health.** Seattle. Wednesday. Center for Occupational Health and Safety. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 623-4801.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

October 17-18—**Alternative Delivery Systems: Strategies for Physician Control.** Washington, D.C. Friday-Saturday. Contact: American Society of Internal Medicine, (202) 289-1700.

October 24—**Twentieth Annual Cancer Conference: Lung Cancer.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

October 29-30—**Focus: Critical Care.** Tacoma. Wednesday-Thursday. Contact: College of Medical Education-Tacoma.

November 6-7—**Current Concepts in Drug Therapy.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

November 7—**Symposium on the Diabetic Foot.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

November 13-14—**Molecular Medicine.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

November 13-14—**Emergency Physicians.** Thursday-Friday. Location to be announced. Contact: American College of Emergency Physicians, Washington Chapter, (206) 441-9762.

November 21-22—**Short-Term Therapy.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

December 4-5—**Worker Health and Safety at Hazardous Waste Site.** Seattle. Thursday-Friday. NW Center for Occupational Health and Safety. Contact: U/W.

December 5—**Practical Pediatrics.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

December 5-6—**Northwest Urologists/Washington State Urology—1986 Annual Meeting.** Tacoma. Friday-Saturday. Tacoma Sheraton. Contact: WSMA.

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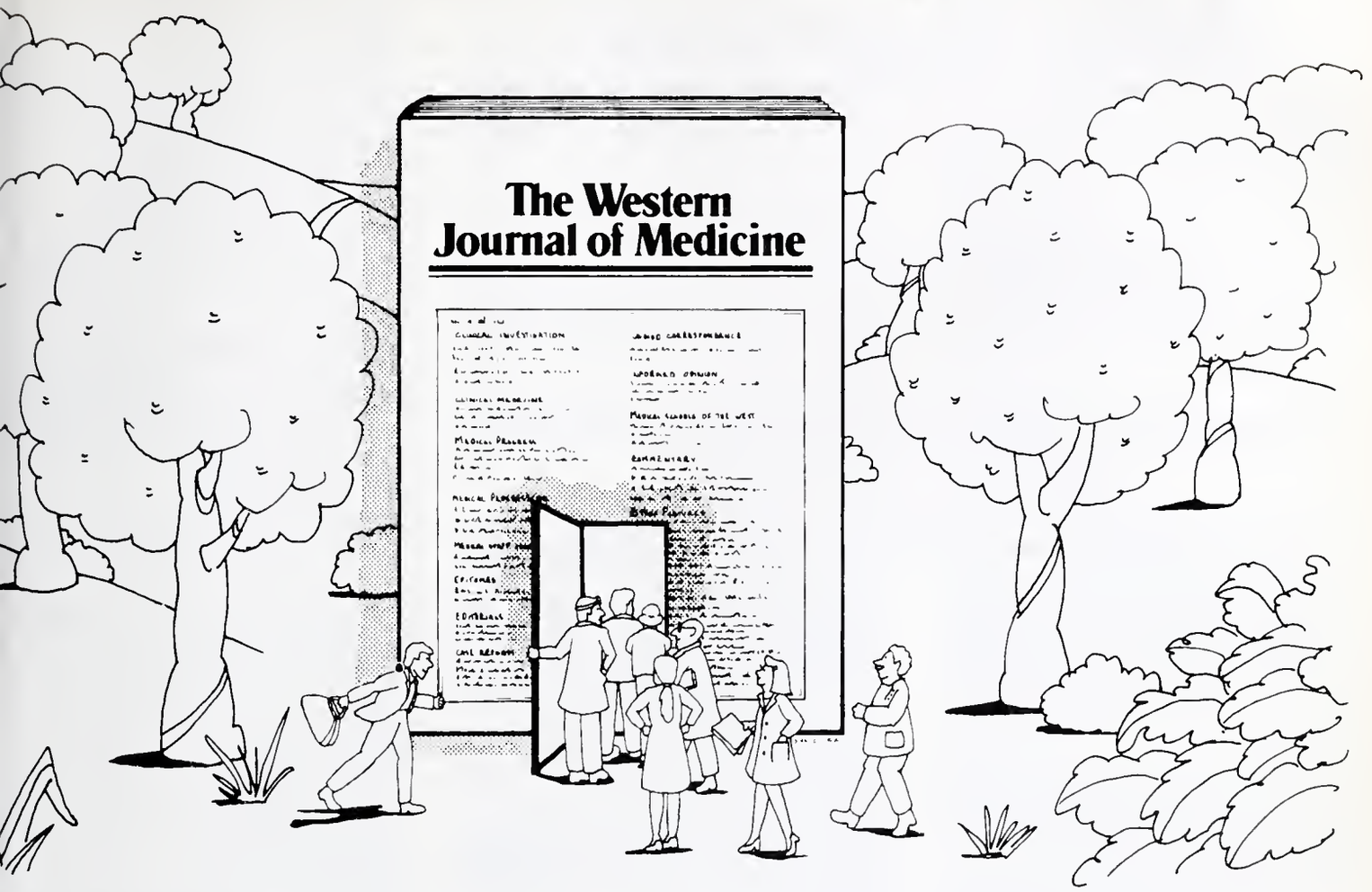

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California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 863-5522. Annual Meeting: March 6-11, 1987, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 18-20, 1986, Snowmass.

Hawaii Medical Association—320 Ward Ave, Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1986, Westin Ilikai Hotel, Honolulu.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 23-26, 1986, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 2-4, 1986, Holiday Inn, Bozeman.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 30-May 3, 1987, Ormsby House, Carson City.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 6-8, 1987, Clarion Four Seasons, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): 1987: Date and place to be announced.

Utah State Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 10-12, 1986, Yarrow Holiday Inn, Park City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 623-4801. Annual Meeting: September 18-21, 1986, Spokane.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1987: Date and place to be announced.

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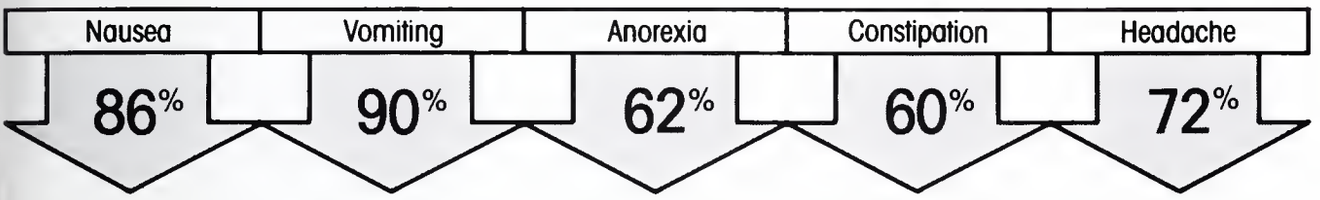

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References: 1. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. **2.** Feighner JP, *et al Psychopharmacology 61*:217-225, Mar 22, 1979

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Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady state concentrations of the tricyclic drugs. Concomitant use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

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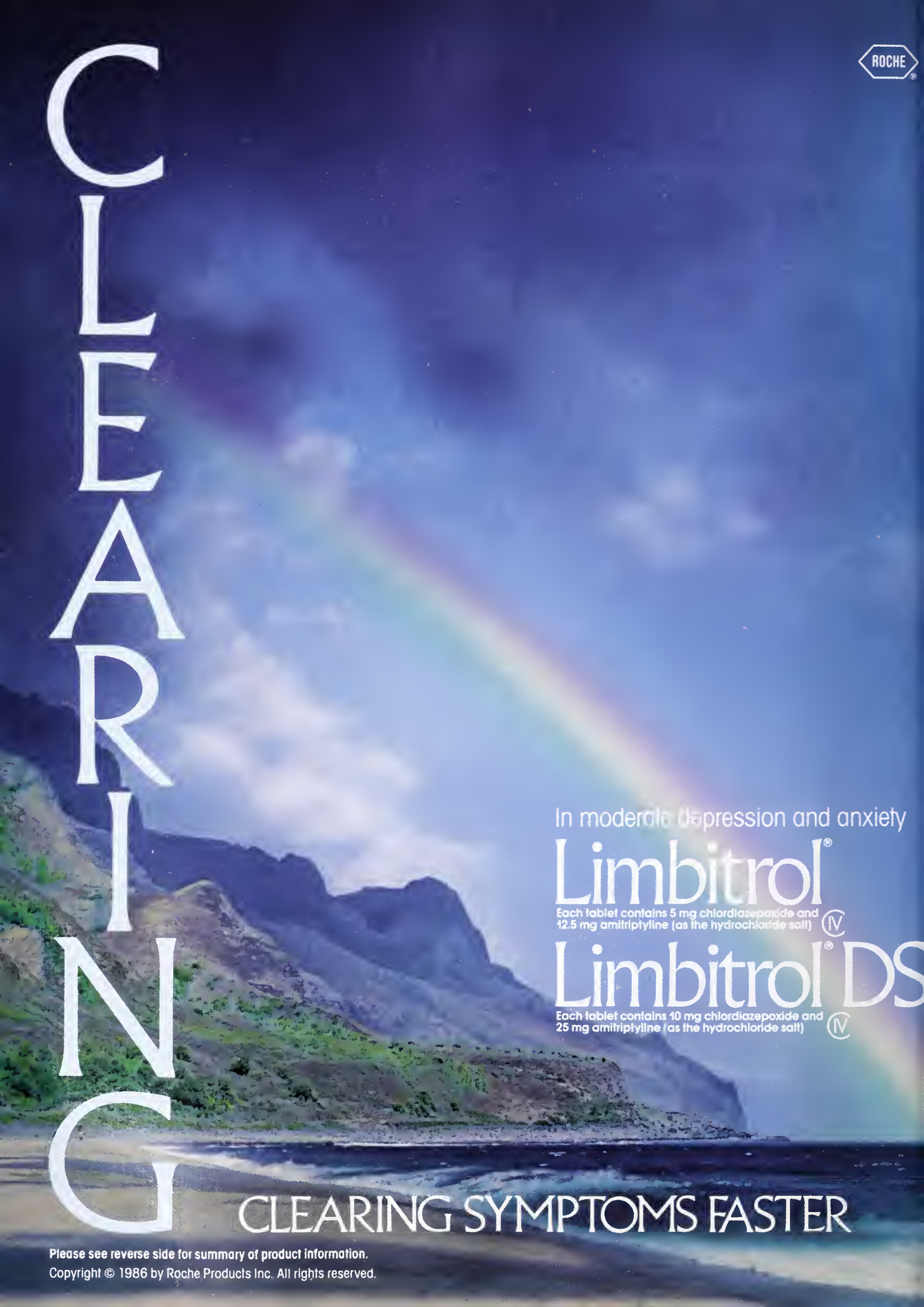

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Precautions: In elderly and debilitated patients, it is recammended that the dasage be limited ta 15 mg ta reduce risk of oversedatian, dizziness, confusion and/or ataxia. Consider patential additive effects with other hypnatics ar CNS depressants. Employ usual precautians in severely depressed patients, or in thase with latent depression or suicidal tendencies, or in those with impaired renal ar hepatic function.
Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientatian and cama, probably indicative of drug intalerance or overdasage, have been reparted. Alsa reported: headache, heartburn, upset stamach, nausea, vomiting, diarrhea, canstipation, GI pain, nervousness, talkativeness, apprehensian, irritability, weakness, palpitations, chest pains, body and jaint pains and GU camplaints. There have alsa been rare accurrences af leukopenia, granulocytopenia, sweating, flushes, difficulty in facusing, blurred vision, burning eyes, faintness, hypatension, shartness af breath, pruritus, skin rash, dry mauth, bitter taste, excessive salivatian, anarexia, euphoria, depressian, slurred speech, cantusian, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase, and paradaxical reactions, e.g., excitement, stimulatian and hyperactivity.
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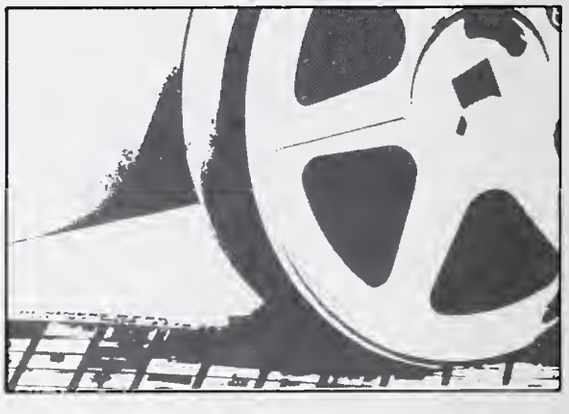

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DESCRIPTION: CORGARD (nadolol) is a synthetic non-selective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2- week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients--Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect; monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 years oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy Category C—In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**— fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE—For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg q.d. (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg q.d. (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information consult package insert.

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References: 1. Alexander JC, Christie MH, Vernam KA, et al: Long-term experience with nadolol in treatment of hypertension and angina pectoris. Am Heart J 108:1136-1140, 1984.

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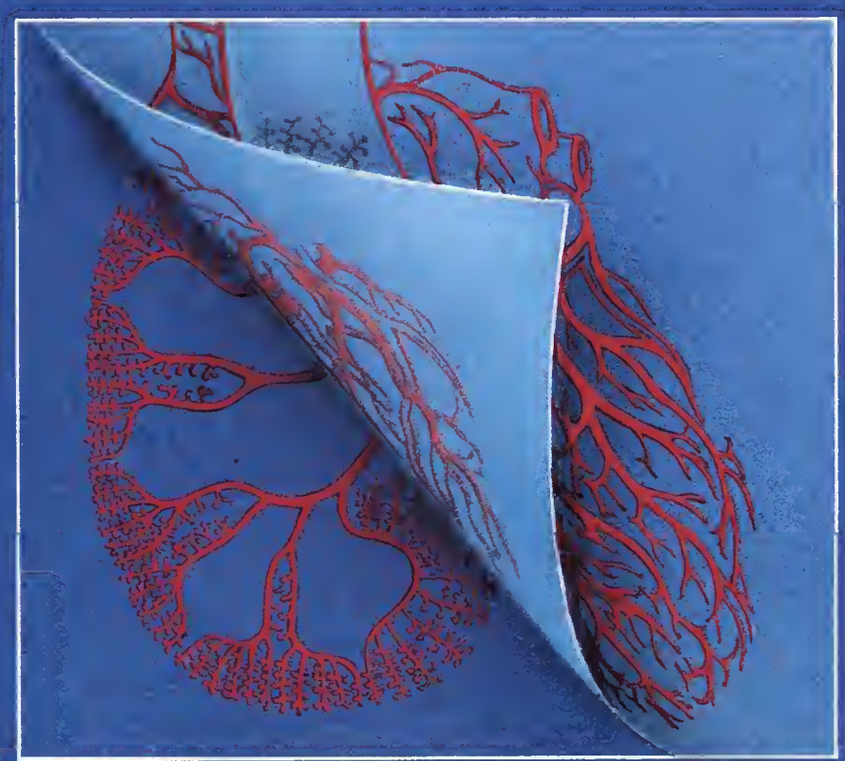

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Vi-Flor® Vitamin/ Fluoride Combination Enhances Compliance

Daily vitamins already containing fluoride make compliance easy and economical for parents.

Regular fluoride updates in the office remind parents of the importance of daily systemic fluoride.

Meet the growing need for fluoride. Prescribe Vi-Flor fluoride vitamins.

See attached statement for full prescribing information.

Mead Johnson
NUTRITIONAL DIVISION

REFERENCES:
[1]Aasenden R and Peebles T: Effects of Fluoride Supplementation From Birth on Human Deciduous and Permanent Teeth. Arch Oral Biol 19:321, 1974.
[2]Hambert L: Controlled Trial of Fluoride in Vitamin Drops for Prevention of Caries in Children. Lancet Feb. 27, 1971, p. 442.
[3]Newbrun, E.: How Fluoride Works: Topical vs. Systemic Action, in Mead Johnson Clinical Report Series, Clinical Importance of Fluoride Nutrition in Infants, Children and Young Adults, Chicago, Pragmaton®, 1985, p. 7.

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Routine VI-FLOR®
supplementation

to help you guard appropriate patients against caries risk and nutritional risk.

INDICATIONS AND USAGE: Prophylaxis of vitamin deficiencies and dental caries in children and adults when fluoride of water supply does not exceed 0.7 ppm.[1,2,3] And, in the case of TRI-VI-FLOR® 0.25 mg Drops with Iron and POLY-VI-FLOR® Drops and Chewable Tablets with Iron, prophylaxis against iron deficiencies. Note: VI-FLOR Drops do not contain folic acid because the vitamin is not stable in liquid form.

PRECAUTIONS: Do not exceed recommended dose or give concurrently with other medications containing significant amounts of fluoride. Prolonged excessive fluoride intake may cause dental fluorosis. All VI-FLOR® with Iron products: as with all products containing iron, parents should be warned against excessive dosage. The bottle should be kept out of reach of children.

Keep all VI-FLOR with Iron products tightly closed and away from direct light.

VI-FLOR Drops should be dispensed in the original plastic container, since contact with glass leads to instability and precipitation.

ADVERSE REACTIONS: Allergic rash has rarely been reported.

DOSAGE AND ADMINISTRATION:

Supplemental Fluoride Dosage Schedule (mg/day)*

Age	Concentration of Fluoride in Drinking Water (ppm)		
	<0.3	0.3-0.7	>0.7
2 wk-2 yr**	0.25	0	0
2-3 yr	0.5	0.25	0
3-16 yr	1.0	0.5	0

*From the American Academy of Pediatrics Committee on Nutrition statement, Fluoride Supplementation: Revised Dosage Schedule. Pediatrics 63(1):150-152, 1979.

**The Committee favors initiating fluoride supplementation shortly after birth in breast-fed infants (0.25 mg F/day). In formula-fed infants, fluoride supplementation should be according to the fluoride content of the water used to prepare formula.

PRODUCT	FORM	SIZE	FLUORIDE mg/dose
POLY-VI-FLOR 0.25 mg	Drops	50 ml Bottle	0.25
POLY-VI-FLOR 0.25 mg with Iron	Drops	50 ml Bottle	0.25
POLY-VI-FLOR 0.5 mg	Drops	50 ml Bottle	0.5
POLY-VI-FLOR 0.5 mg with Iron	Drops	50 ml Bottle	0.5
POLY-VI-FLOR 0.5 mg	Tablets	Bottle of 100	0.5
POLY-VI-FLOR 0.5 mg with Iron	Tablets	Bottle of 100	0.5
POLY-VI-FLOR 1.0 mg	Tablets	Bottle of 100	1.0
POLY-VI-FLOR 1.0 mg with Iron	Tablets	Bottle of 100	1.0
TRI-VI-FLOR 0.25 mg	Drops	50 ml Bottle	0.25
TRI-VI-FLOR 0.25 mg with Iron	Drops	50 ml Bottle	0.25
TRI-VI-FLOR 0.5 mg	Drops	50 ml Bottle	0.5
TRI-VI-FLOR 1.0 mg	Tablets	Bottle of 100	1.0

REFERENCES:

1. Hennon DK, Stookey GK and Muhler JC: The Clinical Anticariogenic Effectiveness of Supplementary Fluoride-Vitamin Preparations—Results at the End of Four Years. J Dentistry for Children 34:439-443 (Nov) 1967.
2. Hennon DK, Stookey GK and Muhler JC: The Clinical Anticariogenic Effectiveness of Supplementary Fluoride-Vitamin Preparations—Results at the End of Five and a Half Years. Pharmacology and Therapeutics in Dentistry 1:1-6 (Oct) 1970.
3. Hennon DK, Stookey GK and Muhler JC: Prophylaxis of Dental Caries: Relative Effectiveness of Chewable Fluoride Preparations With and Without Added Vitamins. J Pediatrics 80:1018-1021 (June) 1972.

VI-SOL®/VI-FLOR® products are the nation's most prescribed children's vitamin and fluoride-vitamin supplements.

(For complete details, please consult full prescribing information.)

Mead Johnson

NUTRITIONAL DIVISION

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Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

INTERPRETIVE MEDICAL MICROBIOLOGY—Edited by Harry P. Dalton, PhD, Professor, Department of Pathology and Microbiology, and Director, Clinical Microbiology Laboratories Medical College of Virginia, Virginia Commonwealth University, Richmond, and Harry C. Nottebart, Jr, JD, MD, Clinical Associate Professor, Department of Medicine, University of Virginia School of Medicine, Charlottesville, and Associate Clinical Professor, Department of Pathology, Medical College of Virginia, Virginia Commonwealth University, Richmond. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 1,040 pages, $115.

INVASIVE PROCEDURES IN CRITICAL CARE—Volume 7 in CLINICS IN CRITICAL CARE MEDICINE—Edited by Charles L. Sprung, MD, Associate Professor of Medicine, University of Miami School of Medicine, and Director, Section of Critical Care Medicine, Veterans Administration Medical Center, Miami, and Ake Grenvik, MD, Professor of Anesthesiology and Surgery, University of Pittsburgh School of Medicine, and Director, Critical Care Medicine, University Health Center Hospitals, Pittsburgh. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 282 pages, $39.

MANUAL AND ATLAS OF FINE NEEDLE ASPIRATION CYTOLOGY—Svante R. Orell, ML, FRCPA, FIAC, Associate Professor of Pathology and Director of Diagnostic Cytology, Flinders Medical Centre, Adelaide, South Australia; Gregory F. Sterrett, MBBS, FRCPA, MIAC, Pathologist, Hospital and University Pathology Services, The Queen Elizabeth II Medical Centre, Perth, Western Australia; Max N-I. Walters, MD, FRACP FRCPath, FRCPA, Professor of Pathology, University of Western Australia, and Director, Hospital and University Pathology Services, The Queen Elizabeth II Medical Centre, Perth, Western Australia, and Darrel Whitaker, PhD, CFIAC, FIMLS, AAIMLS, Cytologist, Hospital and University Pathology Services, The Queen Elizabeth II Medical Centre, Perth, Western Australia. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 232 pages, $139.

MANUAL OF ENDOCRINOLOGY AND METABOLISM—Norman Lavin, MD, Associate Clinical Professor of Pediatrics and Endocrinology, University of California, Los Angeles, School of Medicine, and Director of Perinatal and Pediatric Research, Endocrine Sciences Laboratory, Tarzana, California. Little, Brown and Company, 34 Beacon St, Boston, MA 02106, 1986. 719 pages, $19.50.

MEDICAL ASSESSMENT OF THE ELDERLY SURGICAL PATIENT—Gwyn Seymour, MB, ChB, BSci, MRCP(UK), Senior Lecturer in Geriatric Medicine, University of Wales College of Medicine. Aspen Systems Corporation, 1600 Research Blvd, Rockville, MD 20850, 1986. 315 pages, $37.50.

OB-GYN EMERGENCIES—THE FIRST 60 MINUTES—Edited by Roy G. Farrell, MD, Emergency Physician and Director, Walk-In Emergency Clinic, Group Health Medical Center, Seattle, and Assistant Clinical Professor of Medicine, University of California, Irvine. Aspen Publishers, Inc, 1600 Research Blvd, Rockville, MD 20850, 1986. 330 pages, $37.

ORTHOSTATIC HYPOTENSION—Irwin J. Schatz, MD, Professor and Chairman, Department of Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu. F. A. Davis Company, 1915 Arch Street, Philadelphia, PA 19103-1493, 1986. 126 pages, $30.

PATHOGENESIS OF SKIN DISEASE—Edited by Bruce H. Thiers, MD, Associate Professor of Dermatology, Medical University of South Carolina, and Chief, Dermatological Service, Veterans Administration Medical Center, Charleston, South Carolina, and Richard L. Dobson, MD, Professor and Chairman, Department of Dermatology, Medical University of South Carolina, Charleston, South Carolina. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 623 pages, $95.

PATHOPHYSIOLOGY OF ELECTROLYTE AND RENAL DISORDERS—Edited by H. David Humes, MD, Associate Chairman and Professor, Department of Internal Medicine, University of Michigan Medical School, and Chief, Medical Service, Veterans Administration Medical Center, Ann Arbor, Michigan. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 681 pages, $39 (paperback).

THE PERSISTING OSLER—Selected Transactions of the First Ten Years of the American Osler Society—Edited by Jeremiah A. Barondess, MD, Professor of Clinical Medicine, Cornell University Medical College, New York City; John P. McGovern, MD, McGovern Allergy Clinic, Texas Allergy Research Foundation, John P. McGovern Foundation, Houston, and Charles G. Roland, MD, Jason A. Hannah Professor of the History of Medicine, McMaster University Medical Center, Hamilton, Ontario. Aspen Systems Corporation, 1600 Research Blvd, Rockville, MD 20850, 1985. 318 pages, $45.

PHENYLPROPANOLAMINE—A CRITICAL ANALYSIS OF REPORTED ADVERSE REACTIONS AND OVERDOSAGE—John P. Morgan, MD, Professor and Director of Pharmacology, City University of New York Medical School. Jack K. Burgess, Inc, 2175 Lemoine Ave, Fort Lee, NJ 07024, 1986. 98 pages, $22.50.

PHYSICIAN-SPONSORED HMO DEVELOPMENT—Prepared by Eric R. Wagner and Valerie J. Hackenberg for the American Society of Internal Medicine. ASIM, 1101 Vermont Ave, NW, Suite 500, Washington, DC 20005, 1986. 63 pages, $10 (ASIM members), $15 (nonmembers).

PRACTICAL OBSTETRICAL ULTRASOUND—John W. Seeds, MD, Assistant Professor, and Robert C. Cefalo, MD, PhD, Professor, Department of Obstetrics and Gynecology, Division of Maternal and Fetal Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina. Aspen Publishers, Inc, 1600 Research Boulevard, Rockville, MD 20850, 1986. 185 pages, $33.50.

THE PROGRESSIVE NATURE OF RENAL DISEASE—Volume 14 in CONTEMPORARY ISSUES IN NEPHROLOGY—Edited by William E. Mitch, MD, Associate Professor of Medicine, Harvard Medical School, Brigham and Women's Hospital, and Barry M. Brenner, MD, Samuel A. Levine Professor of Medicine, Harvard Medical School, and Director, Renal Division and Laboratory of Kidney and Electrolyte Physiology, Brigham and Women's Hospital, Boston, and Jay H. Stein, MD, Professor and Chairman, Department of Medicine, and Director, Division of Renal Diseases, The University of Texas Health Science Center at San Antonio. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 283 pages, $55.

FOR HYPERTENSIVE PATIENTS INTOLERANT OF BETA-BLOCKER THERAPY

CONSIDER

VASOTEC®

(ENALAPRIL MALEATE | MSD)

For a Brief Summary of Prescribing Information,
please see last page of this advertisement.

FOR APPROPRIATE PATIENTS WITH MILD TO MODERATE HYPERTEN

IT MAY CHANGE THE WA
YOUR PATIENTS FEEL O

VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product.

NTIHYPERTENSIVE THERAPY

- Certain subjective symptoms such as malaise and drowsiness, which may interfere with physical or mental activity, have not been characteristic of VASOTEC. This may be related to the specificity of action of VASOTEC on the renin-angiotensin-aldosterone system.
- In worldwide controlled clinical trials, VASOTEC was generally well tolerated. The overall percentage of patients reporting adverse effects was comparable to placebo.
- For the most part, adverse effects in clinical trials were mild and transient and usually did not require discontinuation of therapy.

Angioedema has been reported in patients treated with angiotensin-converting-enzyme inhibitors, including VASOTEC (0.2% of patients treated with VASOTEC). Angioedema associated with laryngeal edema and/or shock may be fatal. **If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately** (see ADVERSE REACTIONS).

Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. Therefore, discontinue therapy with a beta blocker only in accordance with the recommendations in the prescribing information for that product. Begin therapy with VASOTEC on the day following the last day of therapy with the beta blocker.

FOR MANY HYPERTENSIVE PATIENTS

ONCE-A-DAY

VASOTEC®

(ENALAPRIL MALEATE | MSD)

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FOR MANY HYPERTENSIVE PATIENTS ONCE-A-DAY

VASOTEC®

(ENALAPRIL MALEATE | MSD)

Contraindications: VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product.

Warnings: *Angioedema.* Angioedema has been reported in patients treated with angiotensin-converting-enzyme inhibitors, including VASOTEC. Angioedema associated with laryngeal edema and/or shock may be fatal. **If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased.

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Neutropenia/Agranulocytosis: Another angiotensin-converting-enzyme inhibitor has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General: Impaired Renal Function:* In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of VASOTEC and/or discontinuation of the diuretic may be required.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia. (See *Drug Interactions.*)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, tongue, difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Neutropenia. Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC® (Enalapril Maleate, MSD) is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC may attenuate potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril, but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

There are no adequate and well-controlled studies in pregnant women. VASOTEC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2677 patients.

The most frequent clinical adverse experiences in controlled trials were: headache (4.8%), dizziness (4.6%), and fatigue (2.8%). For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences was not related to total daily dosage within the range of 10 to 40 mg. The overall percentage of patients treated with VASOTEC reporting adverse experiences was comparable to placebo.

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.6%), rash (1.5%), hypotension (1.4%), cough (1.3%), nausea (1.3%), and orthostatic effects (1.3%).

Clinical adverse experiences occurring in 0.5% to 1.0% of patients in the controlled trials included:

Cardiovascular: Syncope, orthostatic hypotension, palpitations, chest pain.

Nervous System: Insomnia, nervousness, paresthesia, somnolence.

Gastrointestinal System: Abdominal pain, vomiting, dyspepsia.

Other: Dyspnea, muscle cramps, hyperhydrosis, impotence, pruritus, asthenia.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema and/or shock may be fatal. If angioedema of the face, tongue, or glottis occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately (See WARNINGS.)

Hypotension: Combining the results of clinical trials in patients with hypertension or congestive heart failure, hypotension (including postural hypotension and other orthostatic effects) was reported in 2.3% of patients following the initial dose of enalapril or during extended therapy. In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. (See WARNINGS.)

Clinical Laboratory Test Findings:

Hyperkalemia: (See PRECAUTIONS.)

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.)

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in hypertensive patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

In overseas marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

For more detailed information, consult your MSD representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

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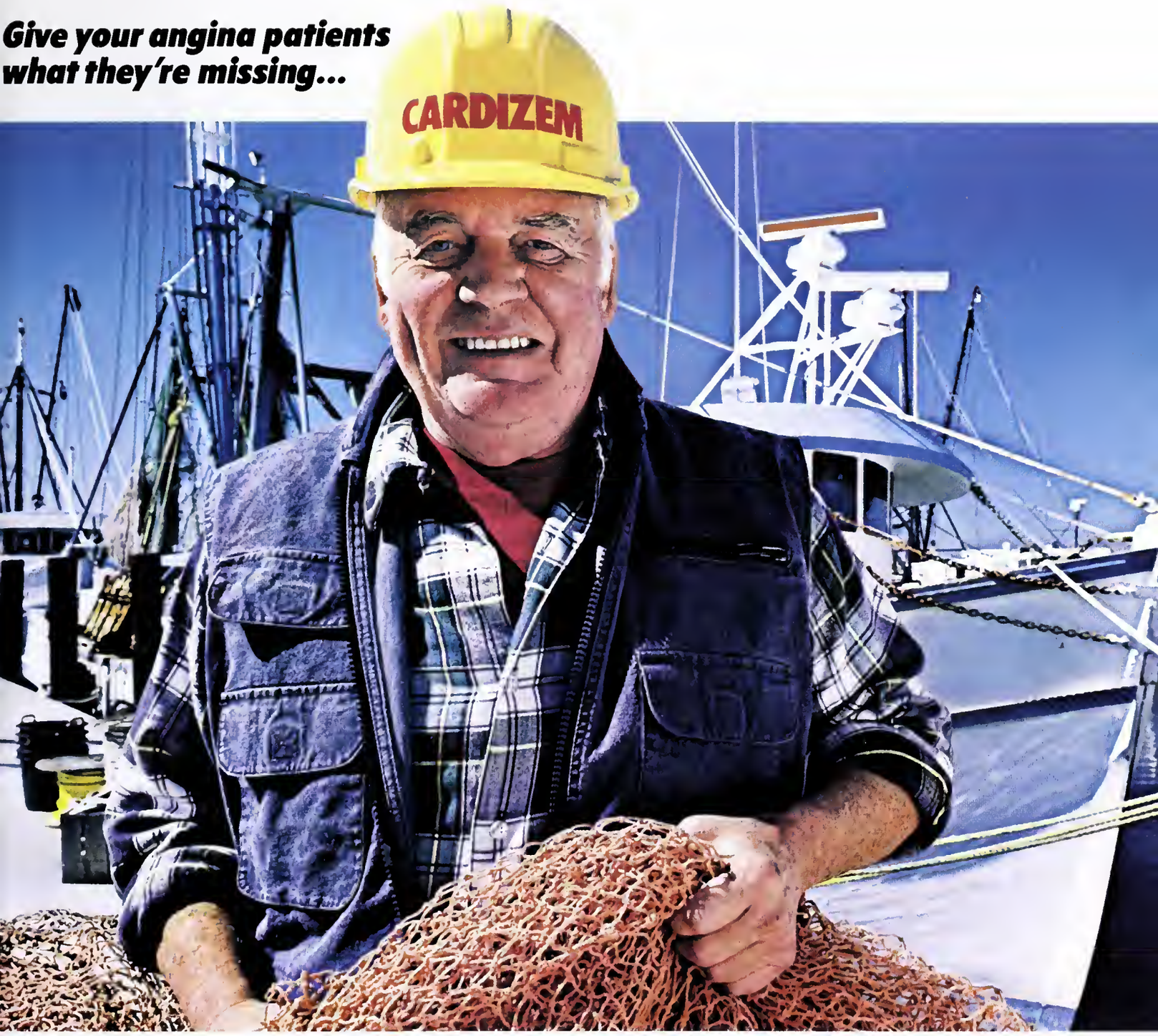
Give your angina patients what they're missing...



CARDIZEM®: FEW SIDE EFFECTS

diltiazem HCl/Marion

- ***Antianginal action includes dilatation of coronary arteries, a decrease in vascular resistance/afterload, and a reduction in heart rate***
- ***Proven efficacy when used alone in angina[1]***
- ***Compatible with other antianginals[2,3*]***
- ***A safe choice for angina patients with coexisting hypertension, asthma, COPD, or PVD[4,5]***

***See Warnings and Precautions.**

Please see brief summary of prescribing information on the next page.

CARDIZEM® FEW SIDE EFFECTS IN ANTIANGINAL THERAPY

diltiazem HCl/Marion

60 mg tid or qid

Brief Summary
Professional Use Information
CARDIZEM®
(diltiazem HCl) 30 mg and 60 mg Tablets
CONTRAINDICATIONS
CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).
WARNINGS

1. ***Cardiac Conduction.*** *CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.*
2. ***Congestive Heart Failure.*** *Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt).*
   Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. ***Hypotension.*** *Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.*
4. ***Acute Hepatic Injury.*** *In rare instances, significant elevations in enzymes such as alkaline phosphatase, CPK, LDH, SGOT, SGPT, and other symptoms consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)*

PRECAUTIONS
General. *CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.*
Drug Interaction. *Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)*
Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.
Carcinogenesis, Mutagenesis, Impairment of Fertility. *A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.*
Pregnancy. *Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.*
There are no well-controlled studies in pregnant women, therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers. *Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.*
Pediatric Use. *Safety and effectiveness in children have not been established.*

ADVERSE REACTIONS
Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.
In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.
The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	*Angina, arrhythmia, AV block (first degree), AV block (second or third degree — see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.*
Nervous System:	*Amnesia, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.*
Gastrointestinal:	*Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.*
Dermatologic:	*Petechiae, pruritus, photosensitivity, urticaria.*
Other:	*Amblyopia, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.*

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established. *Issued 11/85*
See complete Professional Use Information before prescribing.

References: ***1.*** *Pepine CJ, Feldman RL, Hill JA, et al: Clinical outcome after treatment of rest angina with calcium blockers: Comparative experience during the initial year of therapy with diltiazem, nifedipine, and verapamil. Am Heart J 1983; 106(6):1341-1347.* ***2.*** *Shapiro W: Calcium channel blockers: Actions on the heart and uses in ischemic heart disease. Consultant 1984,24(Dec):150-159.* ***3.*** *Johnston DL, Lesoway R, Human DP, et al: Clinical and hemodynamic evaluation of propranolol in combination with verapamil, nifedipine and diltiazem in exertional angina pectoris: A placebo-controlled, double-blind, randomized, crossover study. Am J Cardiol 1985;55:680-687.* ***4.*** *Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39.* ***5.*** *Schroeder JS: Calcium and beta blockers in ischemic heart disease. When to use which. Mod Med 1982;50(Sept):94-116.*

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(Continued from Page 318)

October 27-31—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Monday-Friday. 40 hrs. Fee: $550. Contact: UCSF.

October 27-31—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD at Hanalei Hotel, San Diego. Monday-Friday. Contact: UCSD.

October 31-November 2—**30th Annual Western Occupational Health Conference.** Western Occupational Medical Association at Golden Gateway Holiday Inn, San Francisco. Friday-Sunday. 14 hrs. Fee: $175. Contact: Joe Donovan, WOMA, 433 Palmer Ave, Aptos 95003. (408) 688-9667.

November 16—**Emergencies in Medical Practice.** Granada Hills Community Hospital at Sheraton Universal Hotel, North Hollywood. Sunday. 7 hrs. Fee: $100. Contact: Beverly Chaussee, Granada Hills Community Hospital, 10445 Balboa Blvd, Granada Hills 91344. (818) 360-1021, ext 6789.

December 7-13—**Current Concepts in Emergency Care.** American College of Emergency Physicians at Royal Lahaina Resort, Maui. Sunday-Saturday. 25 hrs. Contact: Georgine Elich, Kailani World Travel, 4192 Meridian Ave, Bellingham, WA 98226. USA (800) 426-2561 or in Washington (800) 562-2597.

December 8-12—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD. Monday-Friday. 32 hrs. Fee: $325-440. Contact: UCSD.

January 12-16—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD at San Diego Hilton Hotel. Monday-Friday. 32 hrs. Fee: $325-440. Contact: UCSD.

February 2-4—**Trauma Management—1987.** UCSD at Hotel Inter-Continental, San Diego. Monday-Wednesday. 20 hrs. Contact: UCSD.

INTERNAL MEDICINE

September 19-20—**Internal Medicine.** Kaiser Permanente Medical Group at Disneyland Hotel, Anaheim. Friday-Saturday. 11 hrs. Fee: $150. Contact: Judy Harrison, Dept of Clinical Services, Southern California Permanente Medical Group, Pasadena 91188. (818) 405-5000.

September 27—**Advances in the Management of End-Stage Renal Disease.** Sutter Community Hospitals at Sacramento Inn. Saturday. 6 hrs. Fee: $70. Contact: Peggy Coit, Sutter Shared Services, 2020 "I" St, Ste D, Sacramento 95814. (916) 446-7684.

October 1—**Angiotensin—Converting Enzyme Inhibitors, New Developments and Current Therapeutic Applications.** Cedars-Sinai Medical Center, Los Angeles. Wednesday. Contact: Lore Kahane, Rm 2049, Cedars-Sinai Medical Center, PO Box 48750, Los Angeles 90048-0750. (213) 855-5547.

October 8—**Gastroenterology—Cholelithiasis and Cholecystitis: New Insights.** LLU at LLU. Wednesday. 4 hrs. Fee: $60. Contact: LLU.

November 8-9—**Transurethral Ureterocopy: A Seminar and Workshop.** UCSD at La Jolla Marriott Hotel, San Diego. Saturday-Sunday. 13.5 hrs. Fee: $375. Contact: UCSD.

November 8-10—**State of the Art Urology—Live Television Coverage of Surgery.** UCLA at Miramar Sheraton Hotel, Santa Monica. Saturday-Monday. 21 hrs. Fee: $400. Contact: UCLA.

November 10-12—**Selected Topics in Endocrinology and Metabolism.** LLU at Ahwahnee Hotel, Yosemite. Monday-Wednesday. 12 hrs. Fee: $225. Contact: LLU.

December 27-January 1—**Advances in Internal Medicine.** University of Washington at Kauai Sheraton, Kauai. Saturday-Thursday. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle 98195. (206) 543-1050.

January 14—**Urology Update.** LLU at LLU. Wednesday. 7 hrs. Fee: $60. Contact: LLU.

February 4-6—**Emerging Technology and Future Trends in Clinical Laboratory Molecular Analyses.** Scripps Clinic and Research Foundation at Vacation Village Resort, San Diego. Wednesday-Friday. 20 hrs. Contact: Bonny Mower, Dept of Academic Affairs, Scripps Clinic and Research Foundation, Box 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

February 8-13—**General Internal Medicine: Concepts and Controversies.** UCSF at Hyatt Lake Tahoe, Nevada. Sunday-Friday. Contact: UCSF

February 12-14—**20th Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. 15 hrs. Contact: UCSF.

OB/GYN

October 2-5—**Advance Fetal Heart Monitoring.** UCI at Napa Valley. Thursday-Sunday. Contact: UCI.

October 10-11—**OB/GYN Ultrasound and Sonography—Update.** Sacramento Radiology Research and Education Foundation and Northern California Radiology Society. Friday-Saturday. 10 hrs. Fee: $125. Contact: John P. McGahan, MD, Sacramento Radiology Research and Education Foundation, PO Box 19184, Sacramento 95819.

October 20-24—**16th Annual Review Course in Obstetrics and Gynecology.** USC at Pasadena Hilton Hotel. Monday-Friday. 38 hrs. Fee: $545. Contact: USC.

THE KUZELL INSTITUTE SYMPOSIA

St. Francis Hotel, San Francisco, California

FRIDAY, NOVEMBER 14

Arthritis: Pathogenesis and Treatment

Inflammation, Robert O. Webster, PhD

Rheumatoid Arthritis, Nathan J. Zvaifler, MD

Remission-Inducing Drugs, Robert F. Willkins, MD

Biotechnology, C. Garrison Fathman, MD

Infectious Agents in Arthritis, Frank R. Schmid, MD

Spondyloarthritis, Andrei Calin, MD

Ocular Inflammation, James T. Rosenbaum, MD

Lyme Disease, Allen Steere, MD

SATURDAY, NOVEMBER 15

Therapeutic Advances in Infectious Diseases

New Antibiotics, Harold C. Neu, MD

The Promise of the Quinolones, Donald Kaye, MD

Infection in the Cancer Patient, Jean Klastersky, MD

Controversies About Prophylaxis and Treatment, Gerald P. Bodey, MD

Anerobic Infections, Sherwood Gorbach, MD

AIDS Symposium, Michael Gottlieb, MD, Paul Volberding, MD, Jack S. Remington, MD, Lowell S. Young, MD

ADMISSION:
No Fee for Attendance

REGISTRATION AND ACCREDITATION FEE:
$15.00/day (Fee includes Category I Credit and Lunch) 6.5 hours Category I—November 14 7.5 hours Category I—November 15

FOR FURTHER INFORMATION:
Division of Education, Pacific Presbyterian Medical Center, P.O. Box 7999, San Francisco, CA 94120, (415) 923-3440

Kuzell Institute for Arthritis and Infectious Diseases
Pacific Presbyterian Medical Center
For Northern California doctors only

CONTINUING MEDICAL EDUCATION

October 20-24—**Comprehensive Review Course and Annual Postgraduate Course.** UCSF at San Francisco Hilton Hotel. Monday-Friday. 32 hrs. Fee: $525. Contact: UCSF.

October 20-25—**9th Annual Review Course in Clinical Obstetrics and Gynecology and/or Gynecological Histopathology.** UCI at Westin South Coast Plaza, Costa Mesa. Monday-Saturday. 17-46.5 hrs. Contact: UCI.

October 25—**Review Course for Gynecologic Pathology.** USC at Pasadena Hilton Hotel. Saturday. 6 hrs. Fee: $105. Contact: USC.

November 1-2—**Changing Trends in Gynecologic Practice.** UCI at Rancho Mirage. Saturday-Sunday. 10 hrs. Contact: UCI.

November 7—**Advances in the Management of Gynecological Cancer.** Sutter Community Hospitals at Sacramento Inn. Friday. 6 hrs. Fee: $70. Contact: Peggy Coit, Sutter Shared Services, 2020 "I" St, Ste D, Sacramento 95814. (916) 446-7684.

December 4-6—**33rd Annual Scientific Meeting—Nebraska OB/GYN Society.** University of Nebraska at MGM Grand Hotel, Las Vegas, Nevada. Thursday-Saturday. 9 hrs. Fee: $200. Contact: Dennis Beavers, MD, 720 N 87th St, Omaha, NE 68114. (402) 390-1200.

December 4-7—**Current Issues in Perinatal Medicine.** UCI at Desert Princess Hotel, Palm Springs. Thursday-Sunday. Contact: UCI.

December 11-13—**Advanced Ultrasound.** American College of OB/GYN at Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. 16 hrs. Contact: ACOG, 600 Maryland Ave SW, Ste 300 East, Washington, DC 20024-2588. (202) 863-2542.

January 16-18—**Gynecology Update for the Primary Care Physician.** UCSD at Vacation Village Resort, San Diego. Friday-Sunday. 15 hrs. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

February 21—**Infertility Update IV.** Scripps Clinic and Research Foundation, La Jolla. Saturday. 6 hrs. Contact: Bonny Mower, Dept of Academic Affairs, Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

(Continued from Page 326)

ACCREDITED SEMINARS on the CONSERVATIVE MANAGEMENT of LOW BACK PAIN

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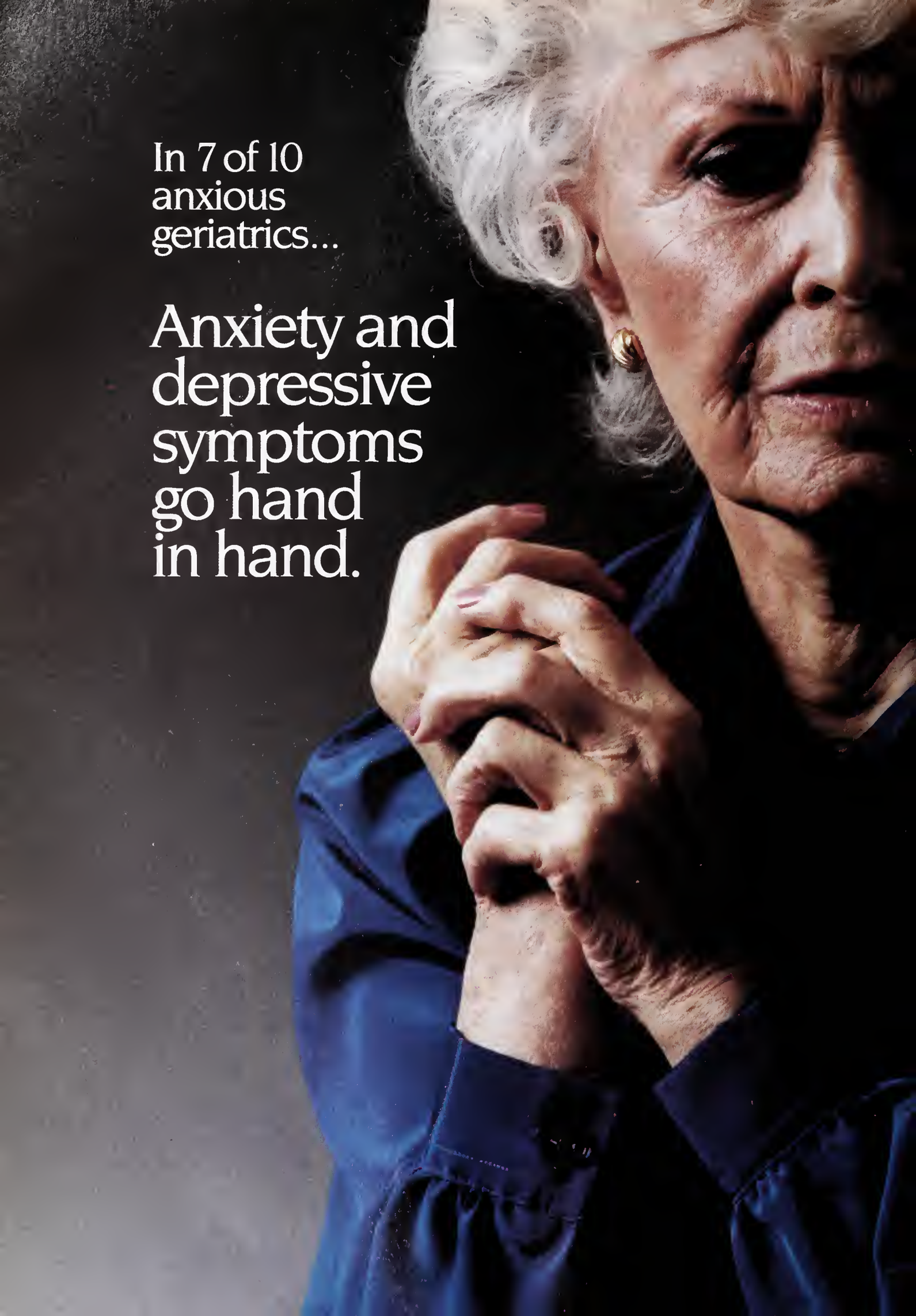
In 7 of 10
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Anxiety and
depressive
symptoms
go hand
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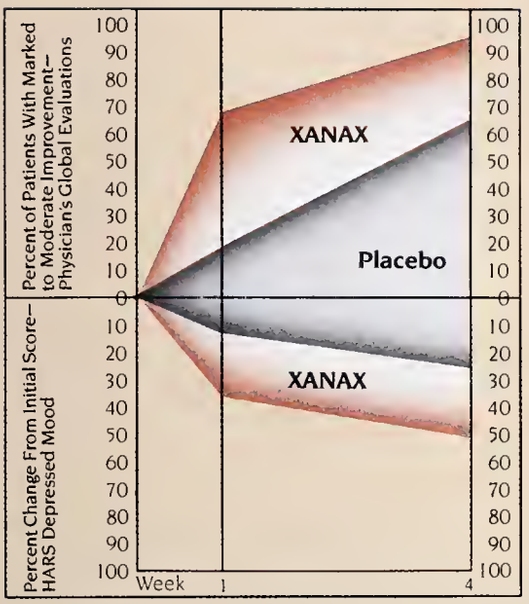
Xanax effectively relieves anxiety with associated depressive symptoms.



In a recent clinical study[1] of 83 geriatric patients with clinical anxiety, 73% were diagnosed as having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than does placebo in reducing the Hamilton Anxiety Rating Scale Total Score and individual items, including depressed mood (see Figure).

With clinical advantages for geriatric patients.

- Effectively relieves the symptoms of anxiety
- Also relieves anxiety with associated depressed mood
- Well tolerated—side effects, if they occur, are generally observed at the beginning of therapy and usually disappear with continued medication. Drowsiness and light-headedness were the most commonly reported adverse reactions
- Does not cause cardiovascular toxicity
- **Specific geriatric dosage**—0.25 mg, two or three times daily

1. Cohn JB: Double-blind safety and efficacy comparison of alprazolam and placebo in the treatment of anxiety in geriatric patients *Curr Ther Res* 1984;35(1):100-112

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Please see adjacent page for brief summary of prescribing information

XANAX® Tablets
(alprazolam) ℞

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, eg, drowsiness or lightheadedness.

Central nervous system. Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes of unknown significance have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION

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January 1986

CONTINUING MEDICAL EDUCATION

(Continued from Page 322)

OPHTHALMOLOGY

September 17-18—**Lasers in Ophthalmology.** UCI at UCI. Wednesday-Thursday. 13 hrs. Contact: UCI.

December 11-12—**An Update in Neuro-Ophthalmology.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Friday. Contact: UCSF.

PATHOLOGY

October 20-25—**9th Annual Review Course in Clinical Obstetrics and Gynecology and/or Gynecological Histopathology.** UCI at Westin South Coast Plaza, Costa Mesa. Monday-Saturday. Contact: UCI.

October 25—**Review Course for Gynecologic Pathology.** USC at Pasadena Hilton Hotel. Saturday. 6 hrs. Fee: $105. Contact: USC.

PEDIATRICS

September 24-25—**43rd Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at the Hilton Hotel, Los Angeles. Wednesday-Thursday. Contact: Eve Black, PO Box 2022, Inglewood 90305. (213) 757-1198.

September 26-28—**Advances in ENT, Allergy, and Infectious Diseases for the Practicing Physician.** American Academy of Pediatrics at Sheraton Palace, San Francisco. Friday-Sunday. 16 hrs. Fee: $330. Contact: AAP, Neal A. Baker, Division of Continuing Education, PO Box 927, Elk Grove Village, IL 60007. (800) 433-9016, or in Illinois (800) 421-0589.

October 16-18—**Practical Topics in Pediatric Nutrition.** UCSF. Thursday-Saturday. 13 hrs. Fee: $300. Contact: UCSF.

October 24-25—**Pediatric Symposium.** Kaiser Permanente Medical Group at Biltmore Hotel, Los Angeles. Friday-Saturday. 12 hrs. Fee: $150. Contact: Judy Harrison, Dept of Clinical Services, Southern California Permanente Medical Group, 393 E Walnut St, Pasadena 91188. (818) 405-5000.

October 25-November 1—**Pediatrics for the Practitioner.** UCI at Mauna Kea Hotel, Hawaii. One Week. 20 hrs. Contact: UCI.

October 31-November 1—**Paroxysmal Disorders of Childhood.** UCSF at Mark Hopkins Hotel, San Francisco. Friday-Saturday. 7 hrs. Fee: $150. Contact: UCSF.

November 13-15—**New Approaches in Children's Orthopaedics.** UCD at Monterey Plaza, Monterey. Thursday-Saturday. 9 hrs. Fee: $340. Contact: UCD.

November 21-24—**8th Annual American Academy**

(Continued on Page 412)

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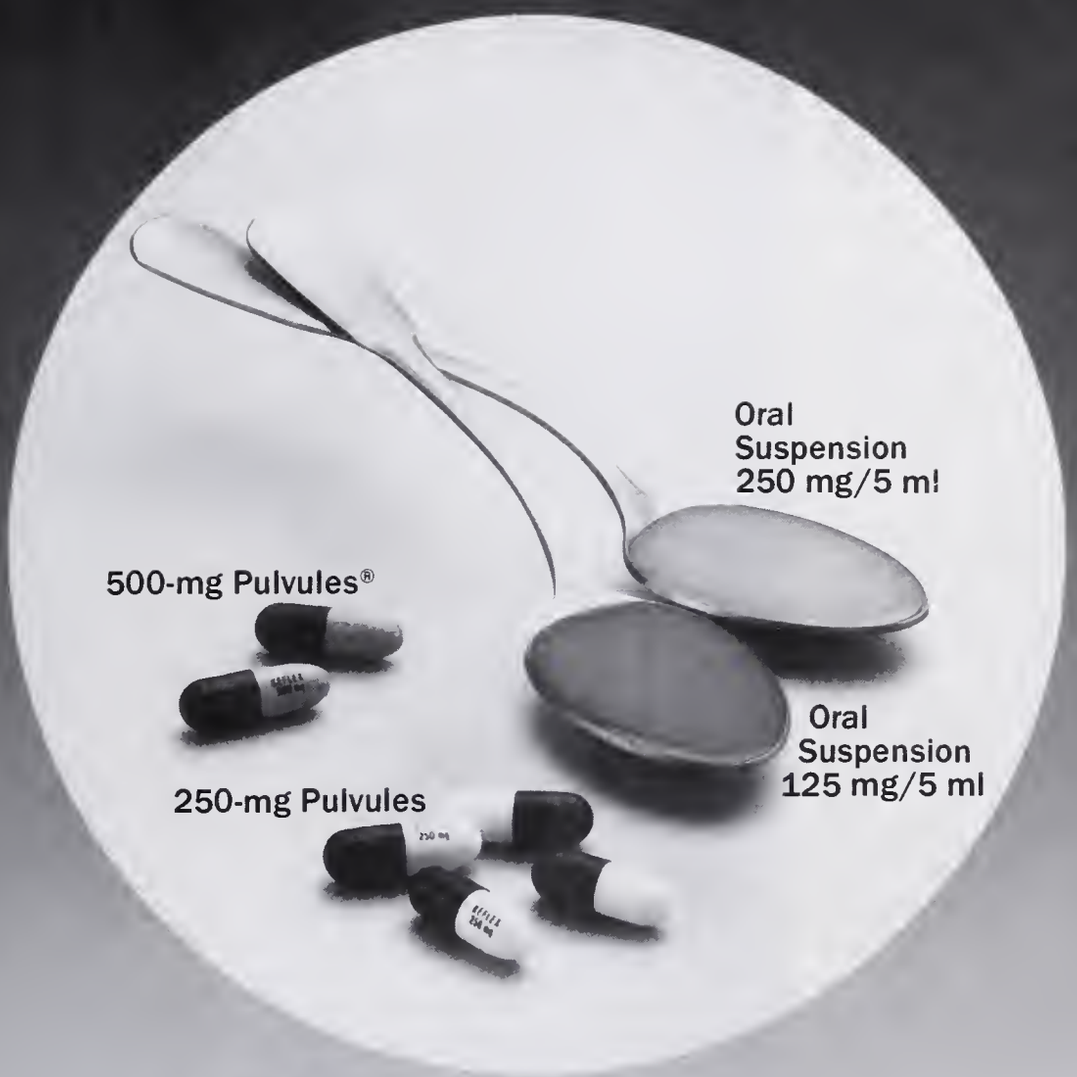

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Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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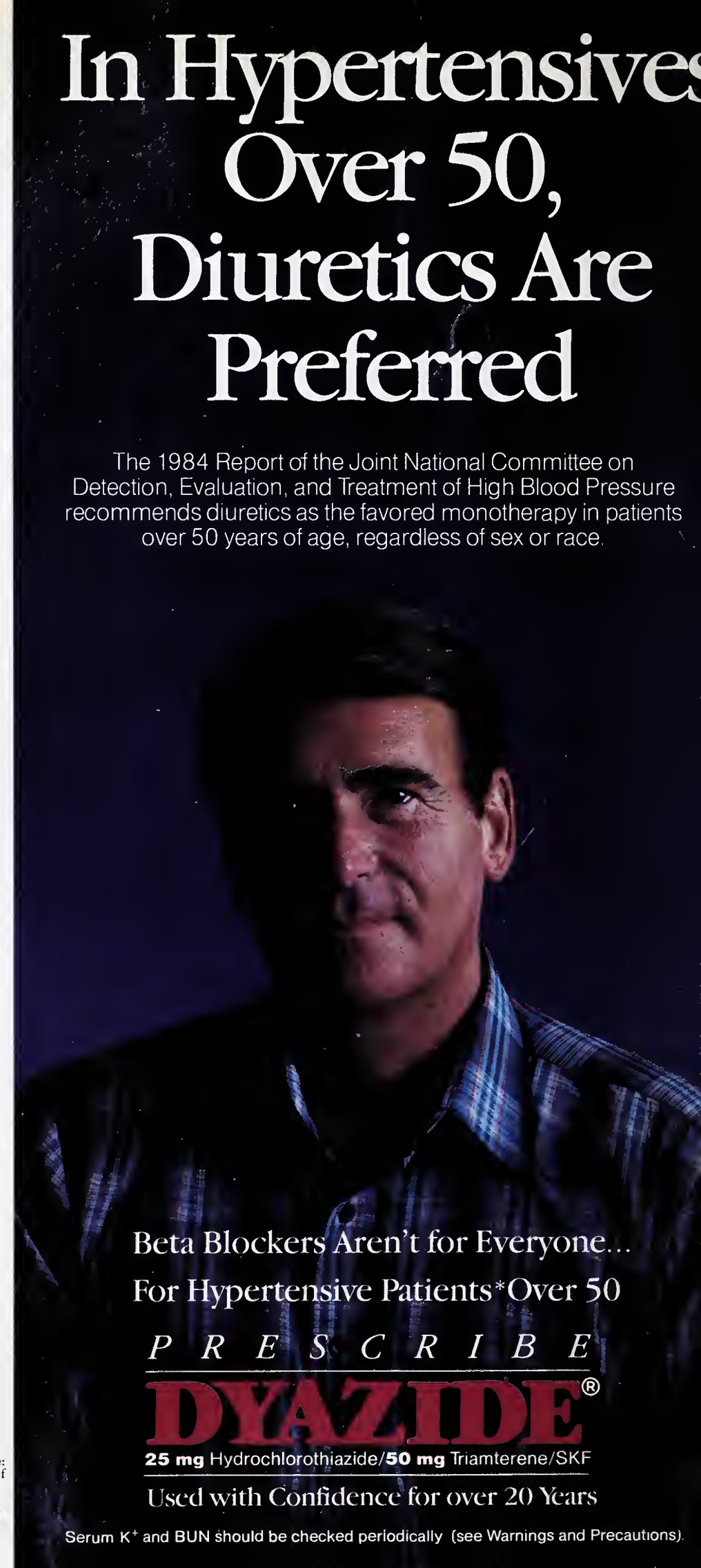
The 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recommends diuretics as the favored monotherapy in patients over 50 years of age, regardless of sex or race.



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Coronary Disease and Risk Factors in Close Relatives of Utah Women With Early Coronary Death

STEVEN C. HUNT, PhD; KURT BLICKENSTAFF, MD; PAUL N. HOPKINS, MD, MSPH, *and* ROGER R. WILLIAMS, MD, *Salt Lake City*

Familial aggregation of coronary heart disease (CHD) and specific major risk factors were determined among 639 first-degree relatives of 73 women with confirmed coronary death before age 55. They were compared with 1,151 persons in 141 control families. Of women with early coronary death, 62% had first-degree relatives with early coronary disease compared with 12% of affected control family members. In the proband families, coronary incidence rates were 2.7 times the control population rates for women ($P < .001$) and 1.6 times the control population rates for men ($P < .05$). An excess incidence of coronary disease was observed for ages 45 to 74 in both men and women.

Smoking, hypertension, diagnosed hyperlipidemia and diabetes were all two to three times more common in the female probands with early coronary death than in healthy controls. Hypertension was more common in all proband relatives (both sexes with and without coronary disease). Smoking was more common among female relatives of probands when compared with the controls.

These data suggest that early coronary disease in women is often familial and associated with smoking and hypertension. The familial aggregation seems to be stronger in female relatives of female probands with early CHD than in male relatives. Genetic factors or shared family life-style or both likely account for these observations.

(Hunt SC, Blickenstaff K, Hopkins PN, et al: Coronary disease and risk factors in close relatives of Utah women with early coronary death. West J Med 1986 Sep; 145:329-334)

It is generally accepted that premature coronary heart disease (CHD) is strongly familial. Most studies showing this have used men as probands or have included few women with CHD. We undertook this investigation to expand this important body of data. The conception of this study parallels work on a set of male probands we have previously described.[1] Reported here are CHD incidence rates in first-degree relatives of women with early CHD and controls and reported risk factor patterns in the two groups of relatives and in a subset of the families selected for pronounced aggregation of early CHD. We hope these efforts will serve to further elucidate factors contributing to the familiality of coronary disease.

Methods

Probands were selected, relatives contacted and data collected in a fashion completely analogous to methods described for our study of male probands with early CHD.[1] Briefly, from 180 Utah death certificates representing all white female Utah residents dying before age 55 of CHD (*International Classification of Diseases* codes 420 for the sixth and seventh revisions and 410 to 414 for the eighth revision) in Salt Lake

From the Cardiovascular Genetics Research Clinic, Cardiology Division, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City.
Supported by National Heart, Lung and Blood Institute grant No. HL21088-09.
Reprint requests to Steven C. Hunt, PhD, Cardiovascular Genetics, University of Utah Research Park, 410 Chipeta Way, Room 161, Salt Lake City, UT 84108.

County between the years 1956 and 1975, data on 73 probands and their families were obtained. Control families were in-laws to the proband family as described previously[1] and shown in Figure 1.

Family informants supplied data for 73 proband families and 141 control families. The informants included 50 proband offspring, 19 proband siblings, 3 proband spouses and 1 parent. The one parent reported only on his wife and offspring and did not provide control information. In each instance where possible, wives or husbands of the informant supplied control family information on an identical set of their own relatives. The 50 offspring informants and their spouses provided control information on up to three nuclear family sets, while the other informants' spouses provided control information on only one family (Figure 1). In all, data for about 41,000 person-years were obtained. Exclusions from the 180 identified probands included 88 probands whose relatives could not be found by phone or mail contacts within the duration of the study and 18 probands with questionable deaths from coronary disease (six with rheumatic heart disease, five with stroke, three with renal failure, two with drug or alcohol overdose and one each with pulmonary embolus and surgical complications of peptic ulcer disease). One person refused to participate.

Data collected for probands, their first-degree relatives and controls included name; birth and death dates and locations; weight status (slender, average, 9 to 22 kg [20 to 49 lb] overweight and 23 kg and more [50-plus lb] overweight); cigarette smoking history (never, former or current), and age at first diagnosis for the following: heart attack, coronary bypass operation or angina pectoris on medical treatment, stroke, diabetes treated with diet or medication, hypertension, elevated serum cholesterol or triglyceride levels and cancer.

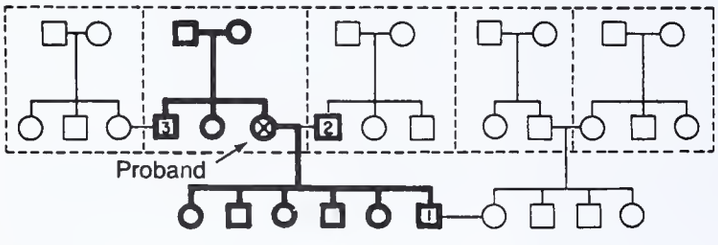


Figure 1.—A pedigree diagram shows the proband families (bold symbols) and matched control families. The three types of primary informants are indicated by numbers in the symbols and include the proband's offspring (1), spouse (2) or sibling (3).

The definition of a positive family history used in this report is identical to that used in our previous study.[1] A family history was positive for CHD if at least two first-degree relatives (not a father and mother only) had CHD, one occurring at a very early age and the other(s) occurring by at least a moderately early age. Very early CHD was, for men, a heart attack by age 55 or treated angina or a bypass operation by age 50. The same events up to five years later were considered very early CHD for women. Moderately early CHD included the same events up to ten years later.

Incidence rates were calculated by adding up the person-years of experience into 15-year age groups. Estimates of relative risk were calculated from the ratio of these rates with exact two-sided 95% confidence intervals calculated by the method described by Mulder.[2] Summary incidence density ratios over age were calculated by the Mantel-Haenszel method.[3]

Results

Familial aggregation of CHD was stronger among women than among men. Striking increases in CHD rates were observed among sisters, mothers and aunts of proband women with early CHD death. Only modest increases of CHD were observed among male first-degree relatives. Incidence rates for CHD death, heart attack incidence and all CHD including treated angina are given in Table 1. Relative risks of CHD comparing male relatives of the probands and controls were significantly greater than 1 for all CHD and all heart attacks, but not for CHD death. The relative risks of CHD for female relatives were significant for all three disease categories. Also, the relative risks for women were consistently higher than the relative risks for men with nearly nonoverlapping 95% confidence intervals, lending statistical support for stronger female than male CHD aggregation in this population. For both male and female proband relatives there appears to be a deficit of relatives with CHD at older ages (75 to 89) compared with the control relatives (Figures 2 and 3), indicating that relatives of female probands with early CHD also tend to have their disease onset at earlier ages. Figures 2 and 3 also show a greater relative increase in CHD risk for

TABLE 1.—*Incidence of Coronary Heart Disease (CHD) in Proband and Control Families**

Age Groups, Years	Total CHD Incidence			All Cases of 'Heart Attack'			Death Due to CHD		
	Proband	Control	RR	Proband	Control	RR	Proband	Control	RR
Men									
30-44	1.8 (6)	1.9 (14)	0.9	1.5 (5)	1.6 (12)	0.9	0.3 (1)	0.7 (5)	0.4
45-59	11.8 (27)	6.3 (36)	1.9	9.4 (22)	6.1 (35)	1.5	4.1 (10)	3.9 (23)	1.1
60-74	29.5 (28)	12.4 (36)	2.4	31.2 (30)	12.0 (35)	2.6	20.9 (22)	9.6 (30)	2.2
75-89	13.8 (2)	40.6 (22)	0.3	6.8 (1)	39.9 (22)	0.2	11.9 (2)	24.6 (15)	0.5
Summary RR and 95% CI†	1.6 (1.3,2.1)			1.6 (1.2,2.0)			1.3 (0.9,1.9)		
Women									
30-44	1.1 (4)	0.8 (5)	1.4	1.4 (5)	0.8 (5)	1.8	0.5 (2)	0.3 (2)	1.7
45-59	5.5 (13)	1.8 (10)	3.1	3.7 (9)	1.1 (6)	3.4	2.5 (6)	0.5 (3)	5.0
60-74	18.0 (21)	3.4 (11)	5.3	17.7 (21)	2.7 (9)	6.6	10.4 (13)	2.1 (7)	5.0
75-89	8.6 (2)	14.9 (12)	0.6	8.5 (2)	13.3 (11)	0.6	11.9 (3)	10.5 (9)	1.1
Summary RR and 95% CI†	2.7 (2.0,3.7)			3.1 (2.2,4.3)			3.1 (2.0,4.6)		

*Incidence rates are new cases per 1,000 person-years (probands are excluded). Numbers in parentheses are number of cases.
†RR = relative risk estimates, CI = two-sided confidence intervals.

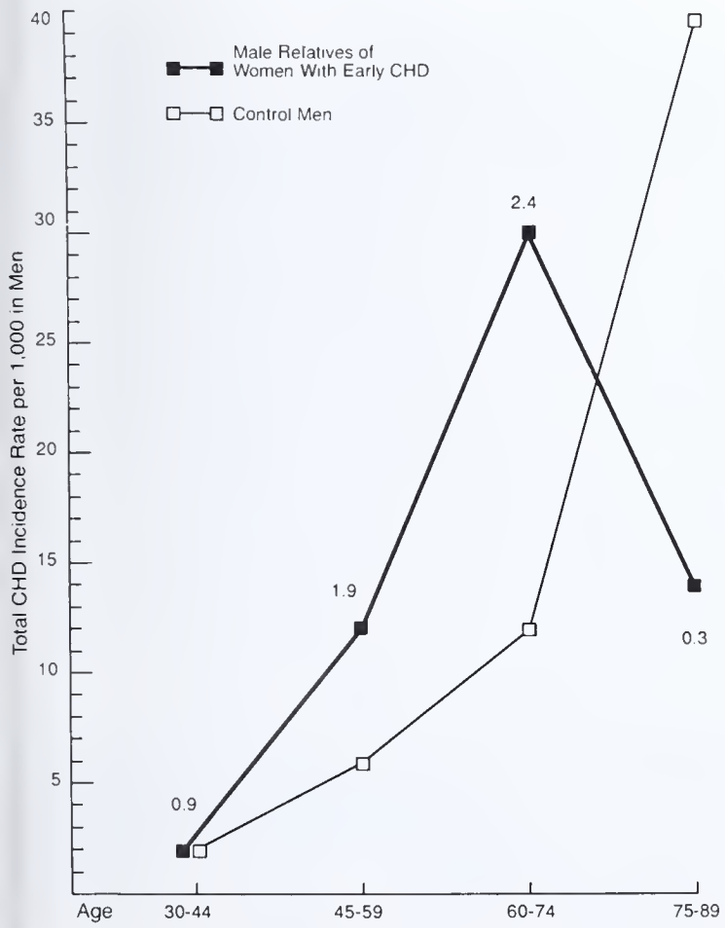
female relatives than for male relatives of each female CHD proband.

Hypertension and cigarette smoking were both more prevalent in the women with early CHD and in their female relatives compared with non-CHD control women as shown in Table 2. These two major risk factors likely account for much of the familial CHD aggregation observed. Within each of the four groups of relatives in Table 2, the proband relatives had a higher prevalence of hypertension than the control relatives, indicating a strong general association of hypertension with a family history of CHD. This higher prevalence of hypertension in the proband relatives was observed even though the proband relatives were younger than the control relatives.

Table 3 shows similar relative risks for CHD among smokers and persons with hypertension in proband and control families. In contrast to the previous study of male CHD proband families,[1] which showed an interaction of smoking and family history—that is, a greater relative risk for smoking among proband relatives than among controls—there was no interaction between cigarette smoking and being related to a female proband in the present study. Similarly, hypertension risk did not interact with being related to the female probands.

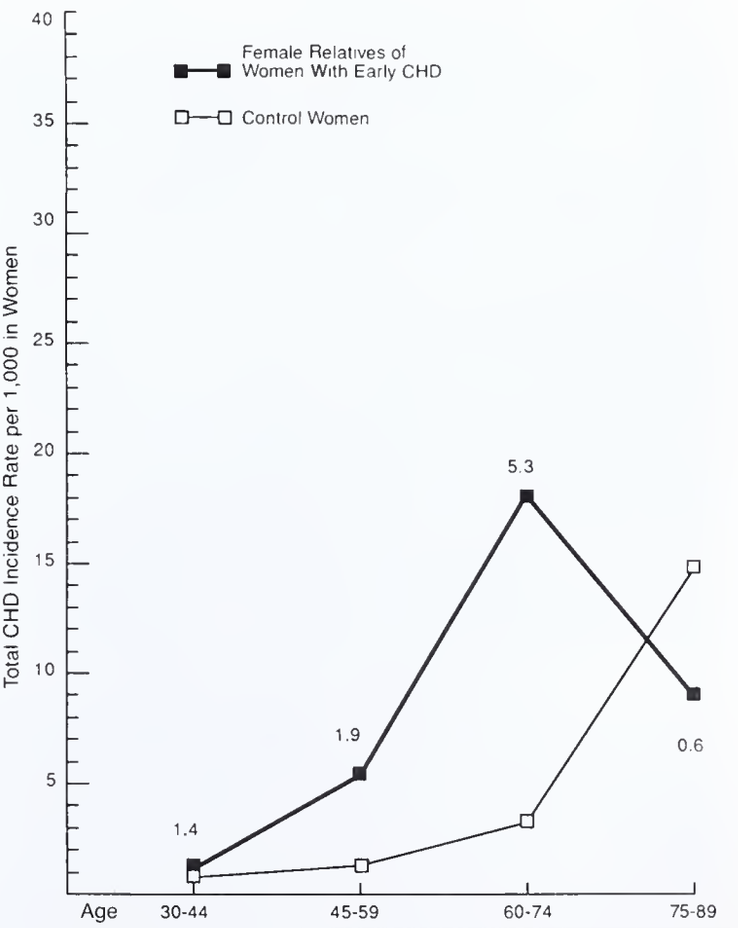
Applying our definition of a positive CHD family history to the 73 proband and 141 control families, we found that 62% of the proband family histories were positive for CHD when probands were included and that 21% were positive when probands were excluded. This compares with only 12% with a positive family history for CHD among the control families.

If a given risk factor is responsible for the aggregation of early CHD in a family, all family members with early CHD would be expected to share that risk factor. To determine the possible contribution of reported risk factors to a familial aggregation of early CHD, concordance was calculated between risk factors and early CHD occurrence. Only those affected persons contributing to the positive family history (two or more relatives per family with very early or moderately early CHD) were included in the concordance tabulations. Probands were included in this table because other affected relatives should share the same risk factors as the proband if there is a common cause of the disease. A family was considered "concordant" for a given risk factor if two



		30-44	45-59	60-74	75-89
Number of CHD Events	■	6	27	28	2
	□	14	36	36	22
Number of Persons at Risk	■	255	191	110	22
	□	519	440	293	96

Figure 2.—Coronary heart disease (CHD) incidence in male first-degree relatives of women with CHD death before age 55 and in control men. Relative risks listed on the graph for each age show about a *twofold increase* in CHD in middle ages for men in the coronary-prone families of female early-CHD probands. By older ages (75-89), few men in the coronary-prone families have CHD, presumably because most of the CHD occurred at an earlier age in these families.



		30-44	45-59	60-74	75-89
Number of CHD Events	■	4	13	21	2
	□	5	10	11	12
Number of Persons at Risk	■	270	204	115	35
	□	469	404	292	123

Figure 3.—Coronary heart disease (CHD) incidence in female first-degree relatives of women with CHD death before age 55 and in control women. Relative risks listed on the graph for each age show a threefold to fivefold increase in CHD in middle ages for women (higher relative risks than in men), suggesting some sex-specificity for underlying risk factor mechanisms. As in men, older women in high-risk families had less CHD than controls.

or more persons with early CHD had the risk factor or, in the case of smoking, if greater than 50% of the affected persons smoked.

Results in Table 4 show smoking and hypertension were the most commonly concordant risk factors—that is, two or more persons with early CHD from families with an early-CHD-positive family history also had hypertension, smoking or both in common. Hyperlipidemia, diabetes and obesity were concordant less often, suggesting, within the limitations of the data, that smoking and hypertension are the most common contributors to positive family histories of coronary disease in families of women with early CHD. More than a third of the coronary cluster families reported no risk factors that could account for their positive family history of CHD. Because the control families in Table 4 are required to have two or more relatives with CHD, they are also families with positive family histories. Therefore, it is not surprising to see a similar concordance of risk factors between the proband and control families.

Discussion

This study of coronary disease and risk factor aggregation in relatives of female victims of early CHD parallels earlier work among male probands and their relatives.[1] In both studies, probands, their families and controls were identified in precisely the same manner. Methods of data collection in the two studies were also identical. The studies, therefore, share the same strengths and weaknesses. Data reliability was assessed in the male proband study where the reporting of CHD end points in the relatives was 89% accurate as verified by death certificates and clinic screening, with no difference between proband and control family reporting accuracy. Reporting of smoking and hypertension was similarly accurate, while reporting sensitivity was below 50% for diabetes mellitus and obesity (>23 kg [50 lb] overweight) and only 24% for hyperlipidemia. Specificity of reporting was greater than 90% for all disease and risk factor data. Although the sensitivity was low for diabetes, obesity and hyperlipidemia, the high specificity made the variables useful and predictive in other analyses of the male and female data (S.C. Hunt, R. R. Williams, unpublished results, May 1984).[1] An association in this study, however, could easily have been missed because of the low sensitivity of these variables.

A major finding in this study was the increased female

TABLE 2.—*Risk Factor Prevalence in Persons With and Without Coronary Heart Disease (CHD) in Proband and Control Families*

Subjects	Number	Mean Age, Years	Prevalence Rates, Percent					
			Smoking	Hypertension	Hyperlipidemia	Obesity	Diabetes	Stroke
Female Proband	73	49	48	27	7	10	14	4
Early Male CHD*								
Proband Relatives	64	61	53	25	9	8	8	2
Controls	102	62	51	15	4	7	13	10
Early Female CHD*								
Proband Relatives	40	60	20	55	3	23	13	13
Controls	38	71	6	42	3	16	29	18
Men Without CHD†								
Proband Relatives	252	44	41	14	2	4	5	3
Controls	507	51	40	9	1	4	4	3
Women Without CHD†								
Proband Relatives	283	47	26	18	2	7	5	5
Controls	504	56	16	13	1	8	4	4

*Early CHD is defined in this table as men with heart attacks before age 60 or treated angina pectoris (including a coronary bypass operation) by age 55. For women, the same events up to 5 years later were considered early CHD. Early female CHD refers to women other than the probands in whom early CHD developed.
†Persons free of CHD at any age.

TABLE 3.—*Associations of Cigarette Smoking and Hypertension With Coronary Heart Disease (CHD) Incidence in Proband and Control Relatives**

Age Category, Years	CHD Incidence in Proband Relatives			CHD Incidence in Controls		
	Smokers	Nonsmokers	Relative Risk	Smokers	Nonsmokers	Relative Risk
30-44	3.0 (8)	0.5 (2)	6.0 (2.6,11.8)	2.0 (9)	1.1 (10)	1.8 (0.8,3.5)
45-59	12.7 (21)	6.3 (19)	2.1 (1.3,3.2)	7.7 (26)	2.6 (20)	3.0 (1.9,4.3)
60-74	22.8 (14)	23.3 (35)	1.0 (0.6,1.7)	8.8 (13)	7.3 (34)	1.2 (0.6,2.1)
75-89	0.0 (0)	13.2 (4)	...	51.3 (10)	20.8 (24)	2.4 (1.2,4.5)
Summary RR and 95% CI			1.6 (1.2,2.2)			2.0 (1.5,2.6)
	Hypertensives	Normotensives		Hypertensives	Normotensives	
30-44	1.7 (3)	1.3 (7)	1.3 (0.3,3.8)	1.9 (4)	1.3 (15)	1.5 (0.4,3.7)
45-59	13.5 (18)	6.6 (22)	2.0 (1.2,3.1)	8.2 (15)	3.3 (31)	2.5 (1.4,4.1)
60-74	36.8 (19)	18.8 (30)	2.0 (1.2,3.1)	10.1 (11)	7.1 (36)	1.4 (0.7,2.5)
75-89	0.0 (0)	13.5 (4)	...	15.6 (4)	27.5 (30)	0.6 (0.2,1.4)
Summary RR and 95% CI			1.9 (1.4,2.6)			1.4 (1.0,2.0)

CI = confidence interval, RR = relative risk

*CHD incidence rates are "all CHD" new cases per 1,000 person-years. Numbers in parentheses are number of affected persons.

aggregation of CHD among female proband relatives. Female relatives of the female probands had a relative risk of 2.7 (2.0 to 3.7 95% confidence interval; $P < .001$) for all CHD compared with control relatives, whereas male relatives of the probands had a relative risk of only 1.6 (1.3 to 2.1 95% confidence interval; $P < .05$). Sex differences in coronary risk among first-degree relatives have been reported by several other authors.[4-11] Most of these studies, however, were focused on early coronary disease in men.[6-11] Data for relatives of female victims of early CHD are scarce. The few studies on relatives of female victims of early coronary death[4,5] had very few female CHD cases reported among the family history data. Even in this study, the confidence intervals for CHD risk in men and women are barely nonoverlapping and do not give definitive answers. Using data from abstracted hospital charts of early CHD death in men and women, we have previously noted a tendency for female relatives of female fatal CHD cases to have a higher risk for CHD than their male counterparts and vice versa.[12] Data from the present study confirm and extend these findings.

When early CHD in women in this study is compared with early CHD in men in our previous study,[1] we find some interesting similarities and contrasts. A positive family history of CHD was present in more than 60% of both men and women with early CHD. Among coronary cluster families, concordance for risk factors suggested smoking and hypertension each may play a major role in about a third of the coronary-prone families. Hyperlipidemia was also implicated for about a fourth of the male proband families but in only 4% of the female proband families. No concordant risk factor was detected for 44% of the coronary-prone families of female CHD probands and for 14% of the families of male CHD probands. Some of these may be due to unknown hyperlipidemia, diabetes mellitus or other factors such as low high-density-lipoprotein-cholesterol levels. The lack of a difference in CHD aggregation between male and female relatives of male CHD probands in our previous study is interesting. In that study, cigarette smoking acted in a possibly synergistic way to elevate the risk among smoking proband relatives. This was true for both men and women.

In families in which smoking interacts with a positive family history of CHD, both men and women may be susceptible to the effects of smoking. For those families in which women have an early expression of CHD in the absence of a smoking interaction, hypertension seems to play the dominant role. The female relatives with CHD of the female probands had hypertension twice as often as the male relatives with CHD, whereas there were less than half as many smokers. Therefore, different risk factors may be involved in the early expression of CHD depending on the sex of the person(s) with the early CHD. In the present study, the only synergistic interaction of risk factors was between female sex and positive family history. There was an excess incidence of hypertension among female relatives of the female probands, especially among those with CHD. There was also an excess of obesity among both probands and control relatives with CHD compared with those without CHD. In the Framingham study, obesity-related risk factors such as hypertension and low high-density-lipoprotein levels were especially strong predictors for CHD among women.[13] One hypothesis suggested by these findings is that a predisposition to CHD may be passed on to female relatives via hypertension due to obesity-related factors whereas among male relatives, a susceptibility to smoking may be more important. Testing these hypotheses will require extensive screening data.

The high prevalence of risk factors reported among female probands in this study is consistent with reports by other investigators.[14-17] In the study by Oliver,[15] of women with myocardial infarction before age 45, 43% smoked, 39% had diastolic hypertension, 48% had hypercholesterolemia, 4% were obese and 2% had diabetes mellitus. Underreporting probably accounts for the relatively few cases of hyperlipidemia among probands (7%) reported for the present study.

Rosenberg and co-workers[18] found in a large sample of female patients with early CHD that 80% were smokers and that smokers had a smaller but significantly increased risk of CHD if they had a positive family history of a myocardial infarction or stroke compared with those who did not have a positive family history. Shea and associates[19] have found that a family history of CHD has a more important role in CHD occurrence in persons who have a lower baseline risk. This may also be the case in our study. Comparing the relative risks of CHD between proband and control relatives (Figures 2 and 3) shows that the relative increase in risk was greater among the women than the men, with the women having a lower baseline incidence of CHD.

Ten Kate and colleagues[20] found that there was no difference in CHD rates between relatives of male CHD probands and relatives of the probands' spouses. The relatives of the spouses had an increased CHD incidence over a group of control relatives, and they suggested that there was assortative mating for CHD risk factors. In both our male and female proband studies, we found an increased CHD incidence in the relatives of the probands compared with relatives of the informants' spouses. Only 17% and 2%, however, of the control families used in our male and female proband studies, respectively, were families of the spouses of the probands. The others were the families of an offspring's or sibling's spouse. They would be more similar to the control relatives used by ten Kate and co-workers than the spouses' relatives and should not be affected by assortative mating unless both the probands' and the informants' spouses were chosen according to the same risk factors.

TABLE 4.—*Risk Factors Associated With a Positive Family History for Coronary Heart Disease (CHD)*

Risk Factors†	Percent of Families With Positive Family History of CHD Showing Concordance for Each Listed Risk Factor*: Proband Families N = 45 (62%)	Control +FH× Families N = 17 (12%)
Smoking	36	35
Hypertension	29	24
Hyperlipidemia	4	0
Diabetes	2	12
Obesity	4	0
None	44	35

*See text in Results Section for definition of risk factor concordance. 62% and 12% are percentages of proband and control families, respectively, with a positive family history (+FH×).

†Risk factor categories are not mutually exclusive. Several families were concordant for more than one risk factor.

Also, the informants themselves were often unaffected by CHD. If there is any assortative mating in our studies of this sort, the magnitude of the results presented would be conservative.

The increased incidence of CHD in families of early CHD probands has important public health implications. Extra emphasis on prevention should clearly be focused on such high-risk families. The fact that potentially modifiable risk factors were concordant with coronary disease in nearly two thirds of these families gives hope that intervention may be especially fruitful in coronary-prone families. On the other hand, the more than one third of families who reported no associated risk factors that could potentially account for their high CHD risk represents a fascinating and challenging group that may provide important insights into the pathogenesis and prevention of the number one killer in the United States and other western nations.

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Thallium 201 Perfusion Imaging After the Treatment of Unstable Angina Pectoris—Relationship to Clinical Outcome

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Unstable angina usually responds to medical management. Unfortunately, a third of patients with this condition may be expected to have severe angina in the ensuing year. We tested the ability of thallium 201 imaging with submaximal exercise to identify patients who have a poor clinical prognosis after an episode of unstable angina. In all, 37 patients were evaluated with ^{201}Tl before hospital discharge and were assessed for severity of angina over the next 12 weeks. Of these, 20 had New York Heart Association class I or II angina during follow-up, 4 of whom had defects on ^{201}Tl imaging that showed redistribution. In 17 patients class III or IV angina developed or they suffered an acute myocardial infarction after hospital discharge, and 15/17 had reversible defects on ^{201}Tl imaging after submaximal stress ($P < .001$). ^{201}Tl scintigraphy frequently identifies areas of ischemia with only submaximal exercise in patients whose unstable angina has responded to medical therapy.

(Hillert MC Jr, Narahara KA, Smitherman TC, et al: Thallium 201 perfusion imaging after the treatment of unstable angina pectoris—Relationship to clinical outcome. West J Med 1986 Sep; 145:335-340)

Myocardial perfusion scintigraphy with thallium 201 has proved to be useful in the diagnosis of coronary heart disease. The demonstration of a ^{201}Tl perfusion defect requires about a twofold (or greater) imbalance of coronary blood flow between two myocardial segments.[1] Imaging a zone of transient ischemia requires a physiologic or pharmacologic intervention sufficient to create such a temporary segmental imbalance in coronary flow. Maximal graded exercise, pacing-induced tachycardia or administration of the coronary vasodilator dipyridamole has been used for this purpose.

Thallium scintigraphy has recently been used for risk assessment in certain subsets of patients with coronary heart disease. ^{201}Tl scintigraphy after low-level exercise testing[2] or a dipyridamole infusion[3] provided important prognostic information in patients with a recent myocardial infarction. Presumably even low-level exercise in a patient after a myocardial infarction may create a coronary flow imbalance sufficient to allow ^{201}Tl imaging of physiologically significant coronary stenoses that may lead to future complications.

Unstable angina pectoris may be a prelude to myocardial infarction or death.[4-8] In addition, while in most patients with unstable angina restabilization can be achieved with medical management, more than one in three patients will suffer from disabling angina in the following year.[9] We have previously found that low-level exercise can be performed soon after stabilization of this syndrome without undue risk and provides useful information. We reasoned that low-level exercise might be sufficient to yield transient ^{201}Tl perfusion defects that could provide important prognostic information in patients soon after stabilization of symptoms, as it had in survivors of myocardial infarction. Testing of the predictive

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ABBREVIATIONS USED IN TEXT
CCU = coronary care unit
ECG = electrocardiogram
NYHA = New York Heart Association

abilities of this technique for the "hard" end points of death and myocardial infarction would require a very large patient sample because of the relatively low frequency of these end points. The incidence of subsequent disabling angina is high, however. Hence, we reasoned that the predictive ability of ^{201}Tl scintigraphy after an episode of unstable angina using this "softer" end point could be tested, as a first step, with a fairly small sample size. Accordingly, the major aim of this study was to assess the frequency of transient ^{201}Tl defects with only low-level exercise soon after stabilization of unstable angina and to test the predictive value of these defects for an unfavorable outcome—death, myocardial infarction or disabling angina—in the 12-week follow-up period after hospital discharge.

Patients and Methods

Patient Selection

In all, 37 consecutive patients, aged 45 to 75 years, who were admitted to the coronary care unit (CCU) of the Dallas Veterans Administration Medical Center or Doctors' Hospital and in whom unstable angina pectoris was ultimately diagnosed were enrolled in the study. The study period ran from July 1980 to January 1983.

Unstable angina was defined as a worsening of previous angina pectoris, a new occurrence of progressive angina pectoris within four weeks before hospital admission or pain at rest. A diagnosis of coronary artery disease was required and was established by one or more of the following criteria: a previously documented myocardial infarction; electrocardiographic (ECG) evidence of myocardial ischemia defined as 1 mm of horizontal or downsloping ST-segment depression 0.08 seconds after the J point; a previously positive ECG stress test in patients with normal resting ST segments; documented coronary artery disease by previous coronary arteriography, or a previous history of typical angina pectoris. Patients who had a possible precipitating event or serious concomitant disease were excluded.

Patients in whom an acute myocardial infarction developed after CCU admission were excluded. An acute myocardial infarction was documented by diagnostic QRS changes or ST-segment and T-wave changes, or both, on the electrocardiogram, consistent with myocardial ischemia in association with elevation of at least two of three "cardiac enzymes" (creatine kinase, aspartate aminotransferase [glutamic oxaloacetic transaminase] or lactic dehydrogenase), to at least twice the upper limits of normal.

Only patients fulfilling these criteria and who were considered responsive to medical therapy were enrolled. Admission medications including nitrates and β-blockers were recorded. Additional sedatives, analgesics, nitrates, β-blockers or calcium blockers were added as deemed appropriate by the attending physicians. Response to medical therapy was considered adequate if a patient was pain free or returned to his or her previous pattern of stable exertional angina pectoris while in hospital. All patients gave their informed consent for the exercise test and scintigraphic study.

Exercise Testing

An upright exercise test was done on a Monark bicycle ergometer in 9 patients or on a treadmill in 28 patients. The electrocardiogram was continuously monitored using a modification of Frank's orthogonal lead system. Recordings at 25 mm per second were made before exercise, during the last 30 seconds of each level of exercise attained and during the first 30 seconds of each postexercise minute of observation (five minutes or until return to preexercise status). Cuff blood pressure recordings were made at one-minute intervals throughout the study. Graded low-level exercise on the bicycle ergometer was done as previously described[10] and on the treadmill according to a modification of the Bruce protocol.[11]

The submaximal exercise test was targeted to a heart rate of 120 beats per minute. Indications for premature termination of exercise[10] included typical angina pectoris, ST-segment changes on an ECG of 1 mm or greater, exercise hypotension and ventricular ectopic activity of grade 2 or higher—that is, more than three unifocal ventricular premature beats per minute, multifocal ventricular premature beats, ventricular couplets or tachycardia or the R-on-T phenomenon. Otherwise, if it was not prematurely terminated by patient fatigue, the exercise test was discontinued at the target heart rate.

Scintigraphic Studies

About one minute before the submaximal exercise was terminated, 2 mCi of thallium 201 was injected intravenously. Myocardial imaging was begun immediately and 200,000 count studies were done in the anterior, 45-degree left anterior oblique and left lateral projections. Three hours thereafter, redistribution images were taken in the same views.

All studies were interpreted by two experienced observers unaware of the patients' clinical status, and a consensus reading was achieved. Results of studies were interpreted as normal, abnormal during stress with subsequent redistribution or abnormal at both stress and redistribution. Areas of redistribution that appeared to be partial were categorized in the same way as those studies with complete redistribution.

Patient Evaluation and Categorization

Patients were evaluated at least once a month for 12 or more weeks after hospital discharge. On each visit, the frequency and duration of angina, nitroglycerin consumption and the patient's report of exercise capacity were recorded and evaluated to define functional class. At the end of 12 weeks, patients were grouped according to their worst anginal status between the time of hospital discharge and the 12-week follow-up evaluation. Anginal status was determined by physicians unaware of the scintigraphic data. Patients with a favorable outcome—that is, those who had no further pain or who had mild stable exertional angina during the 12-week interval (New York Health Association [NYHA] functional class I or II)—were categorized as group A. Patients with an unfavorable outcome, those whose worst anginal status during the 12-week interval was NYHA functional class III and IV or who sustained a myocardial infarction were designated group B. The worst anginal status was used to segregate subjects because all patients were angina free or minimally symptomatic at the time of hospital discharge. While this categorization is based on a subjective

interpretation, it is similar to the clinical evaluation that is commonly applied to assess the adequacy of patient response to a treatment regimen for angina.

Statistical Methods

Group A and group B patients were compared using χ^2 analyses or unpaired *t* tests.

Results

Based on the worst anginal status during the 12-week follow-up period, 20 patients were categorized as group A (no angina or mild stable angina, NYHA class I or II; Table 1) and 17 patients were categorized as group B (severe exertional angina or recurrent unstable angina, NYHA class III to IV or myocardial infarction; Table 2). Two patients had myocardial infarctions but none died during the posthospital evaluation period. The mean age for group A was 61.9 years (range 47 to 75) and for group B was 58.9 years (range 45 to 72).

There were 17 men and 3 women in group A versus 14 men and 3 women in group B. A previous myocardial infarction had been documented in six and seven patients in the respective groups. A prior history of congestive heart failure was noted in one group B patient.

Coronary arteriography had been or was subsequently done in six group A patients, five of whom had three-vessel disease and one who had two-vessel coronary disease. In all, 14 group B patients underwent angiography and 9 had three-vessel disease, 4 had two-vessel disease and 1 had single-vessel disease.

Medications and Hospital Course

There were no major differences in the drug regimens between the two groups. Augmentation or the addition of antianginal medications during hospital stay was determined by the patients' attending physicians. At the time of the submaximal stress test (Table 3), 10/20 of the group A patients were receiving β-blockers (propranolol hydrochloride or metoprolol tartrate), with an average daily dose of 109 ± 48.1 mg per day (mean $\pm$ 1 standard deviation). β-Blocker therapy was being given to all of group B patients at the time of the exercise study. The mean daily dose of β-blocker was 116 ± 106.4 mg per day.

Long-acting nitrates were prescribed in 12/20 group A patients and 14/17 group B patients. Seven group A patients received nifedipine (34 ± 5.4 mg per day). There was no significant difference in the amount of antianginal medications required for individual patients for stabilization in either group, with the exception of more nifedipine therapy in group A. Likewise, there were no significant differences in the duration of hospital stay between groups A and B.

Thallium 201 Scintigraphy

The results of the ^{201}Tl perfusion studies with low-level exercise included nine patients who had a perfusion defect(s) that did not show any diminution when imaging was repeated three hours later, consistent with myocardial infarction. In 19 patients, perfusion defect that totally or partially diminished when imaging was repeated three hours later was consistent with transient myocardial ischemia during the low-level exercise test (Tables 1 and 2). Of these 19 tests showing ischemia, 4 occurred among the 20 group A patients but 15 occurred among the 17 group B patients ($P < .001$). Illustrative examples are shown in Figures 1 and 2. Both patients who suffered a myocardial infaretion during this study had a reversible defect on ^{201}Tl imaging with submaximal stress.

Discussion

The results of the present study show that many patients with unstable angina pectoris have reversible defects on ^{201}Tl imaging. These defects can be seen with only submaximal exercise stress after apparently successful medical therapy. Furthermore, these results show that the presence of a reversible defect is usually associated with an unfavorable clinical outcome in the ensuing three months and that normal findings with ^{201}Tl studies or studies showing stable defects are associated with a more favorable clinical response.

Myocardial Perfusion Abnormalities During Submaximal Stress After Unstable Angina

Deterioration of stable ischemic heart disease to a syndrome of unstable angina pectoris may be caused by transient, reversible limitations in coronary blood flow. This concept is supported by considerable experimental evidence, including ^{201}Tl scintigraphy at rest,[12] and by hemodynamic and angiographic studies.[13-15] Abnormal coronary vasoconstriction or intermittent platelet plugs or thrombi at the site of an atherosclerotic plaque are likely causes of transient limitations in coronary flow.[14-16] When restabilization of the anginal symptoms can be achieved with aggressive medical management, as is the case in most patients, it is likely that the episodes of sudden limitations in coronary flow resolve as mysteriously as they began.

In the past two decades, low-level exercise has been increasingly used in carefully selected patients soon after myocardial infarction to aid in defining prognosis.[17] Detection of ischemia during low-level exercise after myocardial infarction can be enhanced by scintigraphic evaluation of cardiac contractility[18] or myocardial perfusion.[3] In the present study, a strong relationship between ^{201}Tl redistribution and an unfavorable outcome after hospital discharge for patients with unstable angina (group B) was found. We believe that the simplest and most likely explanation for the findings in this study is that ^{201}Tl imaging following low-level exercise identifies, with a high sensitivity, coronary perfusion abnormalities that will result in a poor clinical outeome.

Possible Limitations of the Study

The use of computer-assisted analysis[2] of our ^{201}Tl images might have affected the results of this study. We chose, however, to use visual interpretation of unprocessed images to make the study conditions closer to those generally available in community hospitals.

It is possible that medications played a role in the observed differences in myocardial perfusion between the two groups. The dosage of β-adrenergic blocking agents and nitrates, however, did not differ significantly between the two groups. The use of long-acting nitrates and β-blockers in more group B than group A patients should have favored an effect opposite of the one that we found. While more group A patients had been treated with nifedipine, the doses tended to be low.

Because the choice of medications was left to a patient's attending physician, the increased use of nifedipine in group A patients appears to be coincidental.

A very large patient population would be required to show the ability of this scintigraphic technique to predict hard end points such as death in myocardial infarction. However, the incidence of severe angina pectoris following an episode of unstable angina pectoris is high. Thus, in this study, with ^{201}Tl scintigraphy we identified a large percentage of those patients destined to do poorly despite a relatively small sample size. Finally, coronary arteriography was not done in all patients, which may limit the applicability of our findings.

TABLE 1.—*Clinical Features and Findings in Group A Patients (New York Heart Association Functional Class I or II)*

				Exercise Tolerance Test (Submaximal)				
Patient	*Age, Sex*	*PMI*	*Cath Findings*	*Heart Rate,* beats/min*	*BP,† mmHg*	*ST-Segment Changes*	*Angina*	*Thallium 201‡*
1	52 F	Yes	...	115	170	Yes	Yes	Normal
2	60 F	No	...	120	155	LBBB	No	Normal
3	60 M	No	...	112	170	Yes	No	FD
4	54 M	No	2 V	125	140	No	No	Normal
5	73 M	No	...	115	154	No	Yes	FD
6	61 M	Yes	3 V	110	145	Yes	Yes	FD
7	65 M	No	...	117	135	Yes	Yes	Normal
8	68 F	No	...	100	140	No	Yes	FD
9	67 M	No	...	98	128	Yes	No	Normal
10	66 M	No	...	125	172	No	No	Normal
11	60 M	No	...	93	140	No	No	RD
12	63 M	Yes	...	127	135	No	No	RD
13	59 M	No	...	130	150	No	No	RD
14	75 M	No	3V	122	155	LBBB	No	RD
15	60 M	Yes	...	103	125	No	No	FD
16	65 M	No	...	135	145	Ind	Yes	FD
17	68 M	No	3 V	122	140	No	No	FD
18	48 M	Yes	3 V	78	130	Ind	Yes	FD
19	47 M	Yes	...	118	155	No	No	Normal
20	67 M	No	3 V	92	140	No	No	Normal

Cath = catheterization, Ind = indeterminant, LBBB = left bundle branch block, mmHg = millimeters of mercury, PMI = prior myocardial infarction, V = vessel

*At end of exercise tolerance test.
†Systolic blood pressure at end of exercise tolerance test.
‡FD refers to the finding of a fixed defect on ^{201}Tl perfusion imaging; RD indicates redistribution of a defect on ^{201}Tl perfusion imaging.

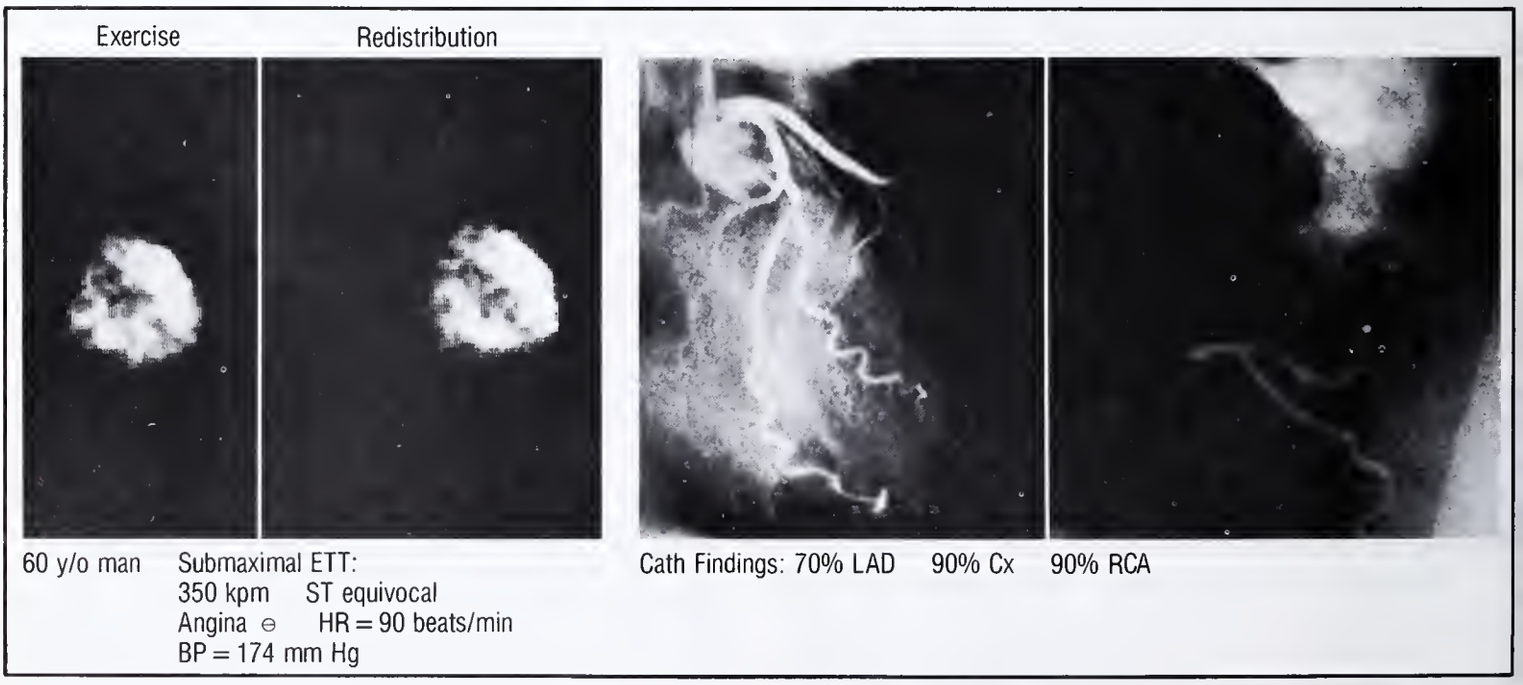

Figure 1.—Submaximal thallium 201 scintigraphy in a 60-year-old man in group A (New York Heart Association functional class I). Despite having three-vessel coronary artery disease, his exercise and reperfusion images are normal during submaximal stress (anterior view shown). The patient was functional class I in the year after this study. BP = blood pressure, Cath = catheterization, Cx = circumflex artery, ETT = exercise tolerance test, HR = heart rate, kpm = kilo-pond-meters, LAD = left anterior descending [artery], RCA = right coronary artery, ST = ST-segment changes

Clinical Implications

Clinical and angiographic findings have been described that can be related to the continued stability of some patients and the deterioration of others after an episode of unstable angina pectoris. In this investigation, class III or IV angina developed in 17 of 37 (46%) patients in the first three months after being admitted to hospital for an episode of unstable angina pectoris. As might be expected, the group B patients had a higher incidence of three-vessel coronary artery disease and prior myocardial infarction than did group A patients. The substantial difference, however, in the eventual outcome of these two groups of patients who recovered from unstable angina pectoris was considerably more apparent when the scintigraphic findings were examined along with the other clinical findings.

Surgical intervention after unstable angina occurs has

TABLE 2.—*Clinical Features and Findings in Group B Patients (New York Heart Association Functional Class III or IV)*

Patient	Age, Sex	PMI	Cath Findings	Exercise Tolerance Test (Submaximal) Heart Rate,* beats/min	BP,† mmHg	ST-Segment Changes	Angina	Thallium 201‡
1	61 M	Yes	3 V	125	152	VPC§	No	FD/RD
2	55 M	Yes	2 V	112	145	No	Yes	RD
3	59 M	Yes	3 V	105	170	No	No	RD
4	59 M	No	2 V	110	130	Yes	No	RD
5	64 M	No	. . .	100	140	Yes	No	RD
6	62 M	No	3 V	122	150	Yes	No	RD
7	61 M	Yes	3 V	96	135	Digll	No	FD/RD
8	63 M	No	3 V	106	145	No	Yes	RD
9	47 M	No	1 V	120	165	No	No	RD
10	72 F	No	3 V	121	185	No	No	RD
11	45 M	Yes	2 V	81	114	No	Yes	RD
12	66 M	No	3 V	112	160	No	Yes	RD
13	50 F	No	. . .	130	140	No	No	Normal
14	59 M	No	2 V	128	172	No	No	FD
15	58 F	Yes	3 V	131	120	No	No	RD
16	72 M	No	. . .	105	145	No	No	RD
17	48 M	Yes	3 V	110	150	No	No	FD/RD

Cath = catheterization, mmHg = millimeters of mercury, PMI = prior myocardial infarction, V = vessel

*Heart rate at end of exercise tolerance test.
†Systolic blood pressure at end of exercise tolerance test.
‡FD refers to the finding of a fixed defect on ^{201}Tl perfusion imaging; RD indicates redistribution of a defect on ^{201}Tl perfusion imaging.
§Test stopped because of ventricular premature beats.
‖Patient was receiving digoxin.

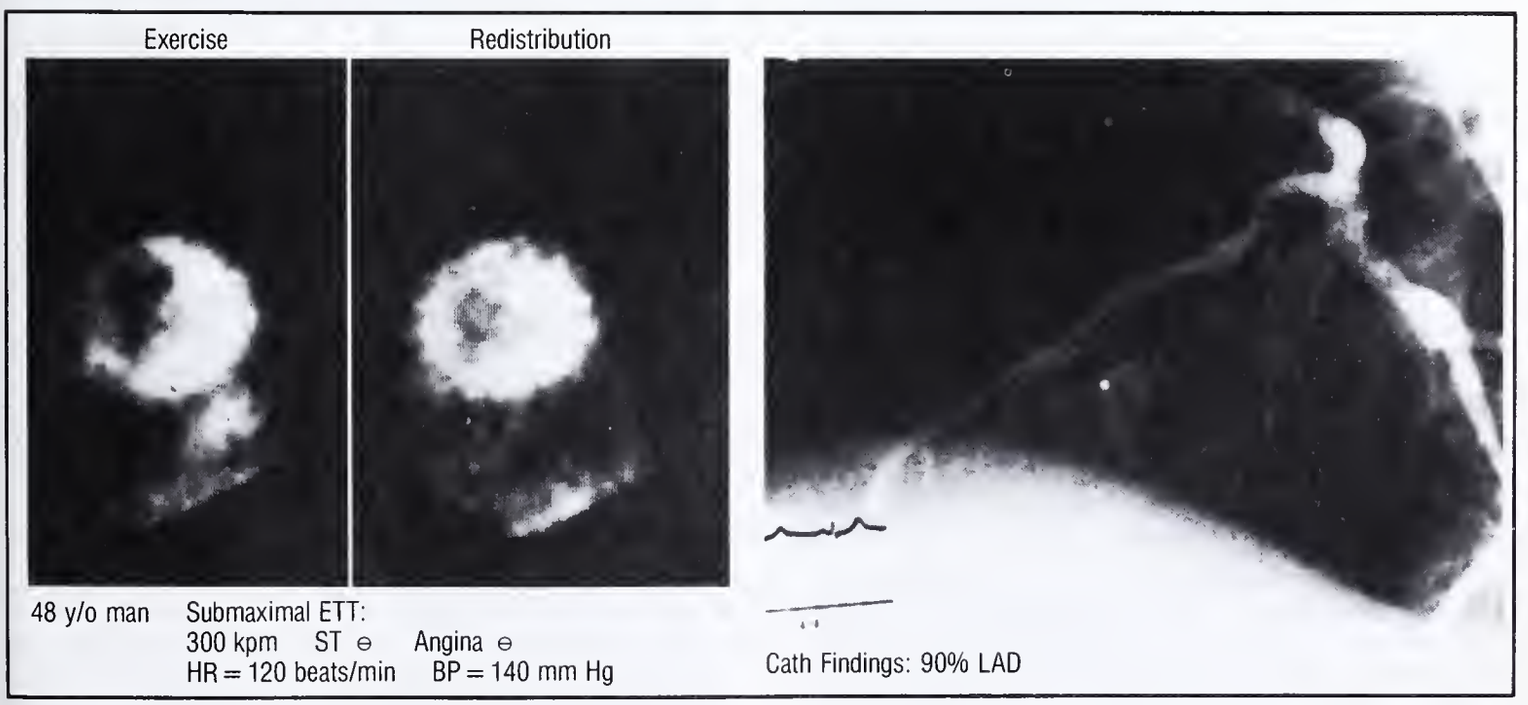

Figure 2.—Submaximal thallium 201 scintigraphy in a typical group B patient (New York Heart Association functional class III or IV). Although he had no angina and completed submaximal testing by reaching his target heart rate of 120 beats per minute, he had a substantial septal perfusion defect with complete reperfusion (left anterior oblique view shown). This patient suffered a nonfatal anterior myocardial infarction 1 month later. BP = blood pressure, Cath = catheterization, ETT = exercise tolerance test, HR = heart rate, KPM = kilo-pond-meters, LAD = left anterior descending [artery], ST = ST-segment changes

TABLE 3.—*Medication Regimen at the Time of Submaximal Stress Testing*

Patients and Drugs	*Group A**	*Group B†*
Patients receiving β-blockers, No.	10/20	17/17
Average daily dose of β-blockers, mg/day	109 ± 48.1‡	116 ± 106.4‡
Patients receiving long-acting nitrates, No.	12/20	14/17
Patients receiving nifedipine, No.	7/20	...
Average daily dose of nifedipine, mg/day	34 ± 5.4‡	...

*Patients with New York Heart Association (NYHA) functional class I or II disorder.
†Patients with NYHA functional class III or IV disorder.
‡± 1 standard deviation.

proved to be effective in decreasing the frequency and severity of angina.[9,19,20] It has been recommended, however, that an urgent coronary artery operation is only indicated in patients who continue to have pain in the hospital despite maximal medical treatment, since surgical therapy in stabilized patients does not decrease the mortality and may increase the incidence of nonfatal myocardial infarction.[9] Yet, coronary artery surgical intervention eventually becomes necessary for more than a third of the patients with coronary artery disease who experience unstable angina.[9,19,20] If those patients who initially respond to medical management but will subsequently require a coronary artery operation for severe angina could be identified soon after the initial episode of unstable angina, the time of disability and its attendant cost could then be limited by earlier bypass surgery or angioplasty.

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Campylobacter Enteritis—A College Campus Average Incidence and a Prospective Study of the Risk Factors for Exposure

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In a prospective study over two years at a university student health center, the average incidence for Campylobacter *enteritis was 4.5 cases per 1,000 students for a nine-month academic year. Male students were more likely to submit a stool specimen for examination and were more likely to have* Campylobacter *enteritis.* Campylobacter *enteritis was ten times more common than* Salmonella *and* Shigella *enteritis combined. The only identifiable increased risk for* Campylobacter *enteritis developing among patients with acute diarrheal illness was the recent ingestion of barbecued chicken.*

(Murray BJ: *Campylobacter* enteritis—A college campus incidence and a prospective study of the risk factor for exposure. West J Med 1986 Sep; 145:341-342)

Campylobacter enteritis is the most common cause of acute bacterial enteritis on college campuses.[1] *Campylobacter* infection is transmitted by the fecal-oral route through contamination of water or food. Household and farm animals can serve as a reservoir, and commonly implicated sources include raw milk, untreated drinking water and undercooked poultry.[2-5]

This prospective study was done over seven academic quarters to determine the average incidence of *Campylobacter* enteritis for a nine-month academic year at one student health service. In addition, it was done to determine if certain risk factors were correlated to *Campylobacter* infection for college students.

Patients and Methods

During seven academic quarters, excluding summers, all stool specimens from patients with acute diarrheal illness were studied. Acute diarrhea was defined as less than ten days' duration and with stools of watery, loose consistency and increased frequency of at least twice normal. All patients were enrolled at the University of California, San Diego, and seen at the Student Health Service.

Fresh stool specimens were typically evaluated within minutes of the time of submission; no rectal swabs were used for collecting stool specimens. A wet-mount study was prepared using one drop of tryptic soy broth mixed with a portion of the liquid feces on a slide. If fecal leukocytes or erythrocytes were seen or if a Hemoccult test was positive, the stool was cultured. The decision not to culture stool specimens with normal microscopic findings was based on previous experience in which return of bacterial pathogens was negligible.[1,6] Over the seven academic quarters, stool specimens were randomly cultured from 30 patients with acute diarrhea who did not exhibit any fecal leukocytes or erythrocytes or have a positive Hemoccult test. The technique for isolating *Campylobacter fetus* subspecies *jejuni* is well described elsewhere.[1,3,6,7] Stool specimens for isolating *Salmonella* or *Shigella* species were inoculated by standard methods.[8]

To evaluate potential risk factors unique for the development of *Campylobacter* enteritis, a questionnaire was completed by all patients with acute diarrhea. The questionnaire inquired about recent foreign travel to Mexico, drinking from mountain streams, recent exposure to domestic animals and any recent consumption of turkey, chicken, barbecued chicken, raw milk or the recent use of a microwave to prepare meat. Results were tabulated and various groups were compared. A χ^2 statistical analysis, with Yates's correction for continuity, was used to compare the groups.

Results

A total of 583 patients (52% men) was seen for complaints of acute diarrheal illness and all were asked to submit a stool specimen. Stool specimens were submitted by 425 (56% men). Men were more likely to submit a stool specimen than women ($P < .0005$; $\chi^2 = 14.6$). A total of 299 stool specimens had positive microscopic findings and they were sub-

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mitted for culture. More than 50% of stools cultured were positive for a stool culture isolate. *Campylobacter* was found in 138 (63% male), *Salmonella* was found in 9 cases and *Shigella* in 5. Men were more likely to have *Campylobacter* enteritis than women ($P < .05$; $\chi^2 = 4.4$). The incidence of *Campylobacter* enteritis for the nine-month academic year was 5.01 per 1,000 in men and 3.84 per 1,000 in women. The overall incidence was 4.5 students per 1,000. *Giardia lamblia* was found in six stool specimens. None of the 30 stool specimens cultured with negative microscopic results had a bacterial isolate on culture.

There were no significant differences between patients with a positive *Campylobacter* stool isolate compared with others with acute diarrheal illness from consuming turkey, chicken, raw milk, mountain stream water or for exposure to domestic animals or use of a microwave to cook meat. There was a significant difference, however ($P < .001$; $\chi^2 = 11.6$), in ingestion of barbecued chicken. Compared with others, patients with *Campylobacter* enteritis were nearly twice as likely to have recently ingested barbecued chicken. There was also a statistical difference for travel to Mexico ($P < .01$; $\chi^2 = 7.7$) between patients with *Campylobacter* enteritis and those with positive stool microscopy but a negative culture. Those with a negative culture were nearly twice as likely to have recently traveled to Mexico.

Discussion

All 30 stool specimens randomly cultured from patients with acute diarrheal illness but with normal microscopic findings on wet-mount examination had negative stool cultures. Consequently, it seems reasonable to conclude that the rate of isolation of *Campylobacter jejuni* would not have been significantly greater if all stool specimens collected had been cultured. Of those patients (425) who submitted a stool specimen, *C jejuni* was found in 32%. Of the 583 patients seen for acute diarrheal illness, 24% had *Campylobacter* enteritis. This is substantially higher than the 4% to 6% found in the general population.[9,10]

The incidence rate of *Campylobacter* enteritis in a nine-month academic year of 4.5 per 1,000 students compares with the finding of 6.0 at another college campus[11] and is higher than the average rate of 1.2 reported by a national college campus survey.[12] The national survey reviewed 231 *Campylobacter* isolates found among 45 different colleges and universities over a single academic quarter. Hence, it may not reflect the true incidence over an entire academic year. The higher yield at this institution is probably in part due to stringent collection methods and rapid laboratory analysis of stool specimens.[6,7] In addition, only patients with true diarrheal illness of an acute nature were evaluated, unlike many studies that review all cases. How many students may have been evaluated by a private physician or had a mild form of *Campylobacter* enteritis not requiring evaluation is unknown.

There was no appreciable difference in seasonal rates for *Campylobacter* enteritis. In this study, however, the isolation rates in the summer were not reviewed because of the then much smaller campus population.

This study, like two other campus studies,[11,13] has elicited a higher incidence of *Campylobacter* infection in men. A review of the frequency of *Campylobacter* enteritis for the past year, however, has shown no statistical difference between the incidence in men and women. Of interest, the national study did not find a higher incidence rate of *Campylobacter* in colleges with a higher percentage of male students.

Reviewing risk factors for exposure showed no increased risk for eating poultry that was not barbecued. Ingesting barbecued chicken, however, was clearly a risk factor. It is well known that a great percentage of poultry, perhaps as much as 90%, harbors *Campylobacter jejuni* organisms.[4,5,14] Adequate cooking will destroy the organism, but barbecued chicken is often not as well cooked as baked, fried or broiled chicken. In addition, applying barbecue sauce with a brush, with continued applications during the cooking process, may serve as a vehicle for contamination. One *Campylobacter* enteritis outbreak has been noted among 11 of 15 who ingested barbecued chicken.[15] The higher observed isolation rate for *Campylobacter* enteritis in the summer[10,16] may well be due to the increased ingestion of barbecued chicken during the warmer outdoor season.

Others have reported raw milk and mountain stream water as possible contagious sources of exposures[4,17,18]; yet, at this campus no identifiable increased association was noted. Travel to Mexico was not more common among patients with *Campylobacter* enteritis. In fact, patients with a negative stool culture and positive wet-mount stool tests were nearly twice as likely to have traveled to Mexico recently. This subgroup of patients probably had travelers' diarrhea, of which enterotoxigenic *Escherichia coli* is the most common etiologic pathogen.[19]

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Drug-Induced Pulmonary Vascular Disease—Mechanisms and Clinical Patterns

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An extensive vascular surface area places the lungs at risk for damage by blood-borne drugs. Drug-induced pulmonary vascular disease may present clinically as acute pulmonary edema, pulmonary edema followed by diffuse interstitial lung disease, pulmonary vascular occlusion, pulmonary hypertension or hemorrhage. It is important to recognize these reactions as drug-related because many are reversible with discontinuation of the drug and supportive therapy. Failure to recognize drug-induced pulmonary vascular disease can lead to significant morbidity and, in some cases, death.

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Recent reviews of drug-induced lung disease have emphasized that drugs can damage specific lung structures (such as airways and pleura) but the mechanisms are generally poorly understood.[1-3] In one area, however—drug-induced lung vascular damage—our insight into mechanisms and clinical patterns has increased recently. This is partly due to increased awareness by clinicians that drugs can injure the lungs, but also because in studies of acute lung injury in vitro and in vivo, drugs were frequently used to damage the lungs and information regarding drug-induced lung diseases was a by-product of such experiments. It has become evident that the lung vasculature is the first bastion of defense against many blood-borne agents and blood vessels may be especially susceptible to injury by some. In this review we will focus on agents with strong experimental or clinical evidence of an association with lung vascular injury. Mechanisms and clinical patterns will be emphasized. We mention specific therapy other than simple drug withdrawal where appropriate. We have included examples of some of the more unusual drug-induced reactions from our own experience.

Mechanisms of Lung Vascular Damage

Increased Microvascular Hydrostatic Pressure

The lungs receive virtually all the cardiac output and are dependent on right- and left-sided heart pressures to distribute this blood flow to the gas-exchange surface. Increased pressure and flow from the right ventricle will more equally distribute blood flow from lung base to apex, but capillaries are somewhat protected from this pressure head by muscular resistance vessels—the arterioles. In contrast, the pulmonary venous bed is less muscular so that increased left atrial pressure is more directly transmitted to pulmonary veins and capillaries and can increase capillary hydrostatic pressure to levels that cause excessive fluid leakage into the lung interstitial space. Lymphatic flow increases in response to increased microvascular pressure and the protein concentration of lung lymph decreases, reflecting the barrier function of the vascular endothelium.[4] If the rate of fluid filtration exceeds the capacity of the lymphatics to remove fluid, interstitial edema will result. Hence, drugs that impair left ventricular function leading to increased vascular pressure of the left side of the heart or lungs or both can cause interstitial pulmonary edema. Drugs that expand intravascular volume and increase microvascular hydrostatic pressure can lead to similar findings.

Increased Permeability of the Vascular Endothelium

The delicate endothelial lining of lung capillaries normally restricts movement of fluid and macromolecules into the lung interstitium, but drugs can injure the endothelium and alter these barrier functions. Toxicity may be direct and due to specific uptake of the drug by endothelium or a lack of enzymes that metabolize the drug, leading to accumulation of the drug or its metabolites in endothelial cells. Alternatively, drug injury may be indirect through interaction with circulating blood cells, especially monocytes, granulocytes or platelets. Vasoactive substances released by these cells may damage the endothelium through activation of the coagulation cascade, stimulation of arachidonic acid metabolism or production of toxic oxygen radicals. Recent evidence suggests that oxygen radicals cause contraction of actin filaments of

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the endothelial cell cytoskeleton leading to increased permeability.[5] Of interest, endothelial permeability may be increased without obvious structural damage detectable by light or electron microscopy.[6] Increased permeability leads to accumulation in lung interstitium of pulmonary edema fluid with a high protein content (similar to that of plasma). If the injury is especially severe, inflammatory and immune effector cells also accumulate in the interstitium. This pathologic process has been termed "alveolitis" and is considered the progenitor lesion of interstitial lung disease.[3] Alteration of the interstitial matrix by the inflammatory process can impair the ability of the lung interstitium to clear fluid and macromolecules.[7] Mechanisms of repair may lead to abnormal accumulation of fibrous tissue in alveolar walls and lung interstitium, especially when the alveolar capillary membrane injury is prolonged and when basement membranes of the alveolar capillary membrane are destroyed.

Vascular Occlusion

Because the pulmonary vasculature functions as a filter for venous blood, embolized solid matter can occlude lung vessels. Drugs are implicated directly and indirectly in such processes. For example, therapeutic or diagnostic agents are directly injected into the venous system and can be trapped by the lung filter mechanism. These agents may activate inflammatory and immune mechanisms that amplify the damage process. Other drugs can be indirect causes of vascular occlusion by stimulating intravascular coagulation (or inhibiting fibrinolysis), which promotes venous clotting and increases the risk of venous thromboembolism.

Impaired Hemostasis

Hemostasis is due to the interrelationship of several factors including the coagulation cascade, platelets, thrombolysis, physical factors (such as the rate of blood flow) and the integrity of the vascular endothelium. Drugs may influence each of these factors and lead to impaired hemostasis. Overt lung hemorrhage is rare but can occur as a consequence of therapeutic anticoagulation or as a serious side effect of treatment with drugs that directly impair hemostatic mechanisms.

Immunologic Mechanisms

Although immunologic processes are thought to be involved in several adverse drug reactions in the lungs, the exact mechanisms involved remain obscure in most cases. Deposition of antigen-antibody complexes on the pulmonary vascular endothelium has been suggested as a possible mechanism of damage because it is known that binding sites for the Fc fragment of immunoglobulin G and for the activated third portion of complement are expressed by endothelial injury.[8] Deposition of antigen-antibody complexes may then trigger a sequence of complement and neutrophil-dependent inflammatory processes that can further damage the endothelium and lead to permeability pulmonary edema and interstitial lung disease.

Alternatively, lung damage may occur as part of a generalized systemic immunologic reaction precipitated by a drug. In this manner, drug-induced lupus erythematosus or systemic anaphylaxis can lead to specific immunologic reactions in which the lungs are damaged as passive bystanders by the inflammatory process directly or by products released (such as lysosomal enzymes) as part of the immunologic reaction.

Clinical Patterns

Pulmonary Edema

Drugs that cause acute pulmonary edema do so by two mechanisms: either by injuring the capillary endothelium causing leakage of fluid and protein into the interstitium of the lungs (permeability pulmonary edema) or by altering hemodynamics that elevate lung microvascular pressure causing increased fluid filtration from vascular to interstitial and alveolar spaces (hemodynamic pulmonary edema) (Table 1). These processes lead to edema fluid with high or low protein concentration, respectively, in animal models of pulmonary edema.[4,7] Both mechanisms, however, may be present concurrently in patients with drug-induced pulmonary edema. Increased permeability of the capillary endothelium will amplify the effect of increased hydrostatic pressure in the microvasculature.

The clinical features of acute pulmonary edema are similar regardless of the pathogenetic mechanism—acute onset of dyspnea with tachypnea and tachycardia, hypoxemia and fluffy infiltrates on the chest x-ray film. A clinician must be alert that drugs may be causal even though a history of drug use may not be immediately available.

Acute permeability pulmonary edema. Salicylates are a common cause of acute permeability pulmonary edema. In most cases patients are older, have ingested the drugs over a long period and have a history of smoking.[9] Smoking may be especially important because it is known to increase the epithelial permeability of the lung,[10,11] possibly predisposing to airspace flooding in the presence of interstitial edema. Proteinuria is commonly present, suggesting that permeability of the renal vascular bed is also increased. The mechanism of salicylate-induced pulmonary edema is not entirely understood, but results of studies in animals confirm increased permeability of the alveolar capillary membrane.[12] Blockade of the cyclooxygenase pathway by salicylates may shift arachidonic acid metabolism to the lipoxygenase pathway leading to production of leukotrienes or hydroxyeicosatetraenoic

TABLE 1.—*Drugs That Cause Pulmonary Edema*

- Permeability Pulmonary Edema
  - Acute
    - Salicylates
    - Opiates
    - Ethchlorvynol
    - Paraldehyde
    - Radiographic contrast media
  - Associated with diffuse interstitial lung disease
    - Bleomycin sulfate
    - Other cytotoxic agents
    - Nitrofurantoin
    - Amiodarone
- Hemodynamic Pulmonary Edema
  - β-Adrenergic blockers
  - Calcium antagonists
  - Doxorubicin hydrochloride, daunorubicin hydrochloride
  - Colloid and crystalloid
- Mechanism Unknown
  - β-Adrenergic agonists

acids, which profoundly increase vascular permeability. Other cyclooxygenase inhibitors (for instance, indomethacin) have been shown to have effects similar to those of salicylates on lung fluid balance.[13] Cyclooxygenase inhibitors may impair platelet function and alter a postulated platelet protective effect on microvascular permeability.[14]

Opiate-induced pulmonary edema is most commonly seen in those abusing narcotics.[15,16] Katz and co-workers reported increased albumin and total protein concentrations in tracheal aspirates from patients with heroin-induced pulmonary edema, suggesting increased capillary permeability.[17] Peterson and associates have suggested that endogenous opioids increase vascular permeability, and exogenous opioids may have a similar effect.[18] Others have found that some patients with opiate-induced pulmonary edema have a low concentration of proteins in edema fluid and reduced clearance of albumin into the alveolar space.[19,20] Also, clinical improvement is often prompt, and radiographic resolution occurs within 48 hours in the absence of infection—points that mitigate against increased permeability and suggest hemodynamic mechanisms. In sum, the bulk of evidence suggests altered permeability as the cause of opiate-induced pulmonary edema, but altered hemodynamics may also be involved.

Ethchlorvynol, a hypnotic-sedative, causes permeability pulmonary edema in humans[21] and animals[22,23] when injected intravenously. The type and severity of reaction varies between species but generally consists of systemic hypotension and reduced cardiac output accompanied by pulmonary hypertension and increased lung lymph flow without change in the lymph to plasma ratio for albumin (suggesting increased permeability). The pulmonary hypertension, but not the interstitial edema formation, can be blocked by indomethacin, suggesting a role of arachidonic acid metabolites in the reaction.[24] Cardiac lymph flow is also increased. Gil and McNiff have shown capillary microthrombi that may cause focal damage and increased permeability in the lungs of rabbits given ethchlorvynol intravenously.[25] Other morphologic studies show that the injury is reversible, limited to endothelial cells in the earliest stages, and consists of subendothelial bleb formation[26] in vivo and retraction of enthothelial cells in culture.[27]

The mechanism of radiographic contrast media-induced pulmonary edema probably includes both permeability and hemodynamic factors. These agents increase endothelial permeability[28,29] but also cause an abrupt increase in the central blood volume. Recent studies suggest that the permeability mechanism may be predominant in animals and that ionic media have a greater risk than nonionic preparations.[30] As would be expected, the effect on extravascular lung water accumulation is greater in the presence of increased left atrial pressure.[31]

Paraldehyde has also been reported to cause permeability pulmonary edema,[32] but there is not enough information to warrant speculation on the mechanism involved.

Permeability pulmonary edema followed by diffuse interstitial lung disease. Pulmonary edema followed by diffuse interstitial lung disease and fibrosis has been described in association with a number of agents, but bleomycin sulfate and nitrofurantoin (Furadantin) have been studied in detail. Initially pulmonary edema is not as severe as the acute permeability edema described above and is followed by accumulation in the lung interstices of inflammatory cells. In most cases, there is widespread damage to alveolar structures, including small arterioles and venules, interstitial cells and matrix, and to cells of the alveolar and small airway epithelium. Bleomycin causes interstitial lung disease by either inhaled or intravenous routes in experimental animal models.

Several considerations suggest that vascular injury is of primary importance. First, the drugs are administered to patients parenterally and thus reach the lungs via the vasculature that must provide the first bastion of defense. Second, there is morphologic evidence from animals and pathologic studies of patients that these drugs damage the lung vasculature at the earliest stages of disease. Finally, pulmonary edema is an early morphologic finding, which implies that loss of the barrier function of the vascular endothelium to fluid and macromolecules is a critical early feature. Thus, the mechanism of lung injury is similar to that of acute permeability pulmonary edema—injury to the capillary endothelium. The injury is generally longer lasting, however, because these drugs are given long term over weeks or months in contrast to agents causing acute pulmonary edema in which the exposure is often massive and short term.

The use of bleomycin causes subendothelial blebs in larger pulmonary arteries and veins as the earliest finding of toxicity, followed shortly by pulmonary edema and damage to type I pneumocytes.[33] There is evidence that both lung endothelium and epithelium are prone to damage because of low levels of enzymes that inactivate bleomycin.[33] In addition, a convincing body of experimental data suggests that toxic oxygen radicals participate in the inflammatory process. Bleomycin toxicity is worsened by concomitant exposure to hyperoxic conditions,[34-36] and lung injury due to bleomycin is attenuated by prior exposure to either hypoxia[37] or endotoxin,[38] conditions known to increase the protective antioxidant mechanisms of the lungs. Because bleomycin interferes with postmitotic processes of cell differentiation, the normal repair processes are impaired and delayed, factors increasing the likelihood of pulmonary fibrosis. Destruction of the alveolar capillary basement membranes, which provide a framework for cellular repair, may be the crucial factor leading to pulmonary fibrosis.

Pulmonary edema and diffuse interstitial lung disease are features of the lung damage caused by several other cytotoxic agents, including cyclophosphamide (Cytoxan), busulfan, nitrosoureas and zinostatin, suggesting a mechanism similar to that of bleomycin involving the lung vasculature, but there is insufficient evidence to warrant this conclusion at this time and further study is needed.

Nitrofurantoin, although less well studied, has many similarities to bleomycin. Toxicity is accentuated in animal species by a hyperoxic environment and lessened by concomitant administration of agents that are scavengers of oxygen radicals.[39] The drug can directly stimulate production of superoxide radicals in lung endothelial cells.[40] Nitrofurantoin can also cause a reaction resembling hypersensitivity pneumonitis, an allergic reaction including pulmonary infiltrates and eosinophilia,[41] but the predominant toxic reaction pattern is pulmonary edema and diffuse interstitial lung disease.

Amiodarone, an iodinated benzofuran derivative used to treat refractory ventricular arrhythmias, causes diffuse inter-

stitial lung disease—in as many as 28% of patients receiving the drug, a reduced diffusing capacity for carbon monoxide develops.[42] The mechanism of toxicity is not clear, but the drug is concentrated in lung parenchyma in vivo and may interfere with phospholipid metabolism since intracytoplasmic lamellar inclusions are found, especially within lysosomes of macrophages, type II pneumocytes, interstitial and endothelial cells.[43] While pulmonary edema has not been described in the early stages of drug toxicity, therapeutic serum concentrations cause intracytoplasmic lamellar inclusions in endothelial cells in vitro and slightly higher levels damage the cells,[44] suggesting that endothelial damage may be an early manifestation of drug toxicity.

Hemodynamic pulmonary edema. Hemodynamic pulmonary edema is caused by drugs that either have a negative inotropic effect on cardiac function or expand intravascular volume—factors that increase capillary hydrostatic pressure in the lungs and favor increased fluid filtration into the interstitial space. Colloid and crystalloid given intravenously for the rapid expansion of intravascular volume are well-known causes of iatrogenic pulmonary edema.

β-Adrenergic blockers, most commonly propranolol hydrochloride, exert a negative inotropic effect on left ventricular function and have been implicated in pulmonary edema, generally in patients with underlying heart disease. Sympathetic mechanisms are vital components of the compensatory responses of the circulatory system, so that blockade of adrenergic receptors in subjects with borderline left ventricular function can further compromise cardiac function. Surprisingly, cardiac norepinephrine stores and β-adrenergic receptors are depleted in patients with heart failure, so it is critical to maintain the function of those remaining receptors.[45] Patients occasionally may require β-agonists for support until the β-blocker is metabolized and excreted in the urine. A unique predilection for propranolol-induced pulmonary edema has been reported in patients with pheochromocytoma,[46,47] possibly due to the unopposed α-adrenergic effects resulting in increased cardiac afterload.

The calcium channel blockers nifedipine and verapamil also have negative inotropic effects and the former has been implicated in pulmonary edema.[48] Diltiazem, another calcium channel blocker, does not adversely affect left ventricular function[49] and should not have similar effects. The antiarrhythmic agents quinidine, procainamide hydrochloride and disopyramide, although not specifically implicated in cases of pulmonary edema, have all been reported to depress ventricular performance, especially disopyramide.[50] Use of these drugs in patients with impaired left ventricular function should be closely monitored.

The cytotoxic drugs doxorubicin hydrochloride[51] and daunorubicin hydrochloride[52] cause a dose-dependent cardiomyopathy with attendant decline in ventricular function leading to pulmonary edema in advanced cases. Also deserving mention is a recent report of a case of pulmonary veno-occlusive disease that occurred following therapy with bleomycin, mitomycin and cisplatin.[53] This disorder is clinically indistinguishable from hemodynamic pulmonary edema.

Mechanism unknown—β-adrenergic agonists. The mechanism of β-adrenergic agonist-induced pulmonary edema is unclear (Figure 1).[54] These drugs, given to inhibit uterine contractions in preterm labor, cause maternal pulmonary edema in 1% to 5% of patients.[55] The clinical picture is often complicated by massive fluid and crystalloid administration, corticosteroids (given to accelerate fetal maturation), hypokalemia and increased cardiac output due to β-agonist effects. Myocardial performance assessed by M-mode echocardiography improves with administration of β-adrenergic agonists during labor,[56,57] and left atrial dimensions are unchanged in patients with pulmonary edema due to these agents. Measurements of pulmonary artery wedge pressure have been normal in several patients studied,[54,58,59] providing further evidence that myocardial performance is not impaired and suggesting that increased pulmonary vascular permeability may be the mechanism of pulmonary edema. But the edema resolves quickly in most patients when the drugs are withdrawn and diuretic therapy given—features more characteristic of hemodynamic edema. Furthermore, β-agonists have been reported to protect against the development of increased permeability in some models of lung vascular injury.[60] Thus, the mechanism of β-agonist pulmonary edema remains unresolved.

Pulmonary Vascular Occlusion

Of the drugs causing pulmonary vascular occlusion, oral contraceptives are most common. Most physicians are aware of the fourfold to sevenfold increase in risk of venous thromboembolism in women taking oral contraceptives.[61,62] Prolonged administration of higher doses (more than 50 μg) of estrogens carries a significantly greater risk. The mecha-

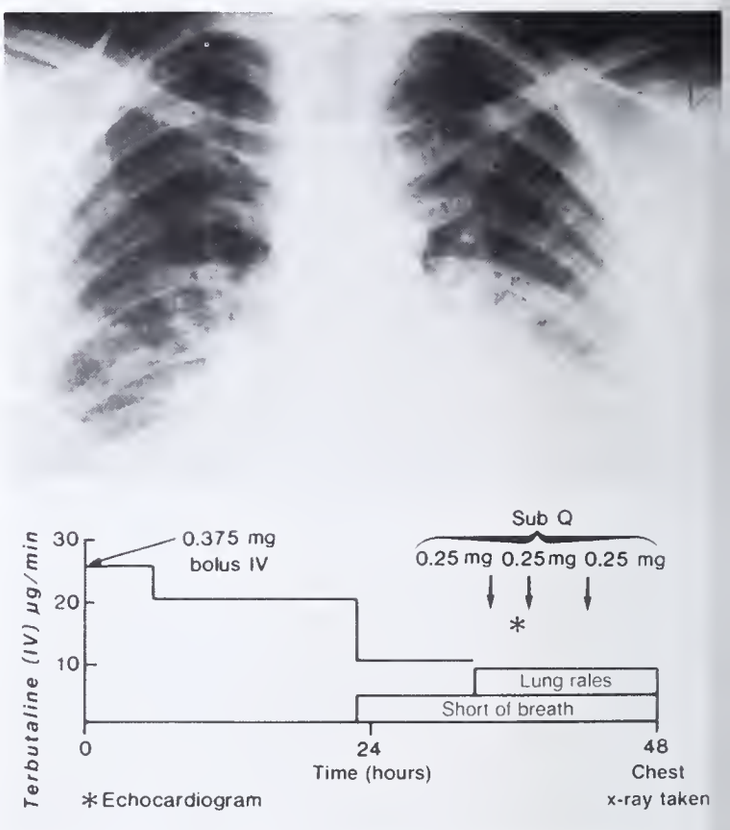

Figure 1.—Acute pulmonary edema during terbutaline infusion given to inhibit preterm labor in a 32-year-old pregnant (32 weeks) woman. A chest roentgenogram shows fluffy perihilar densities that cleared after diuretic and oxygen therapy. The inset shows the sequence of intravenous (IV) and subcutaneous (Sub Q) terbutaline therapy and the appearance of symptoms and signs of pulmonary edema. An echocardiogram was done during the period of respiratory distress and showed normal left atrial size and left ventricular function.

nisms responsible for this effect have not been elucidated, but estrogens are known to increase platelet adhesiveness and decrease venous tone. Estrogens have recently been reported to cause vascular endothelial cells to exert a procoagulant effect.[63]

Less well described is the risk of pulmonary vascular occlusion following therapeutic embolization procedures—especially those involving arteriovenous malformations. Arterial embolization with Gelfoam, silicone spheres or fluid, polyvinyl alcohol foam, metal springs and even isobutyl-2-cyanoacrylate (Super Glue, Figure 2) have been used to occlude arteriovenous malformations, vascular tumors and bleeding vessels.[64]

Pulmonary embolization with the use of ethiodized oil occurs in most, if not all, patients undergoing lymphangiography and has also been described as a rare complication of hysterosalpingography, urethrography or myelography. Symptoms (dyspnea, cough, fever) or radiographic signs (interstitial granular stippling), however, occur in slightly more than half of patients (Figure 3).[65-68] An increased dose or rate of administration increases the incidence of symptoms, and patients with preexisting lung diseases, especially of the vascular bed, are at increased risk.[69] Pulmonary edema[70] and hemorrhage[71] have also been described and occasionally result in the adult respiratory distress syndrome.[72] The mechanism of lung injury has been postulated to be direct damage of the alveolar capillary membrane by free fatty acids.[73] Ethiodized oil contains conjugated oleic and linoleic acid that can be broken down to the free fatty acids by lipoprotein lipase on the surface of the vascular endothelium, causing increased permeability[74] or direct injury[75] to the vascular endothelium. The body's inflammatory response to the oil may also have a role because proteases and vasoactive mediators (such as histamine and kinins) are released by leukocytes in the process of oil ingestion.[70]

Pulmonary Vasculitis

Foreign material such as talc, starch, cellulose and maltose are used as filler for tablets and capsules taken orally. Drug abusers sometimes inject suspensions containing these substances intravenously, causing a foreign body granulomatous reaction centered around blood vessels (Table 2). A chest film may be normal or show abnormalities ranging from nodular densities to the appearance of progressive massive fibrosis.[76] Most patients have slowly progressive disability and a portion die of cor pulmonale.

Pulmonary vasculitis is a feature of the eosinophilic pneumonia caused by several drugs including nitrofurantoin,[77] sulfonamides, penicillins, hydralazine hydrochloride[78] and procainamide hydrochloride.[79] This disorder, formerly included in the pulmonary infiltrates and eosinophilia syndrome, is

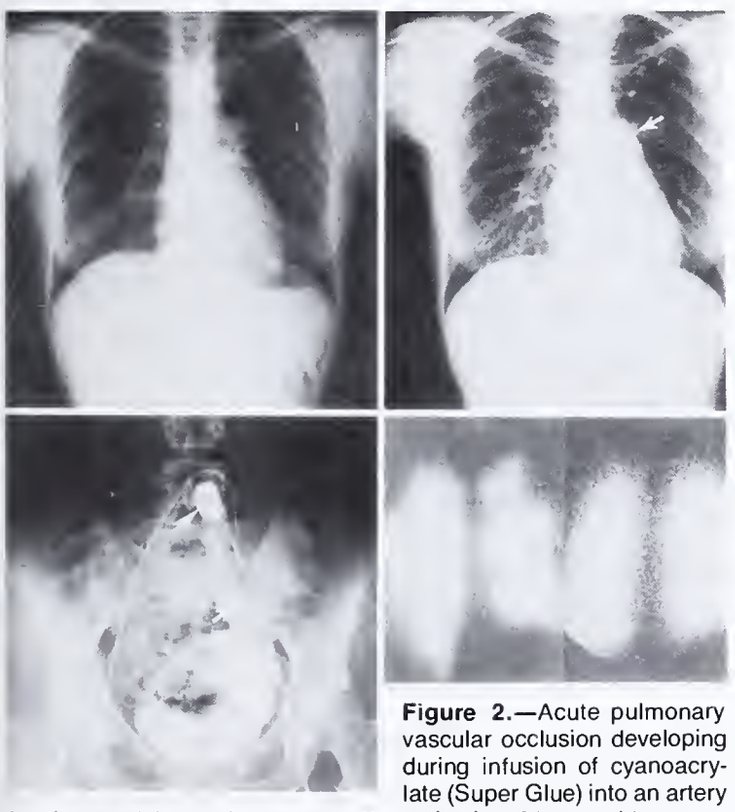

Figure 2.—Acute pulmonary vascular occlusion developing during infusion of cyanoacrylate (Super Glue) into an artery feeding a pelvic arteriovenous malformation in a 31-year-old woman. Upper left panel shows a normal chest roentgenogram taken before angiography. Lower left panel shows roentgenogram of contrast dye injection into left ovarian artery **(small arrow)** before cyanoacrylate infusion. Note balloon catheter in left iliac vein **(large arrow)** impeding venous return from the arteriovenous malformation. The patient became acutely dyspneic and complained of chest pain during infusion of cyanoacrylate. Upper right panel shows chest roentgenogram during dyspneic episode. Note enlarged main **(arrow)** and right pulmonary artery shadows indicating pulmonary hypertension. Lower right panel shows ventilation **(right)** and perfusion **(left)** lung scans showing multiple segmental perfusion defects and normal ventilation.

Figure 3.—Lymphangiogram using contrast media (ethiodized oil [Ethiodol]) shows complication of pulmonary vascular occlusion. A chest roentgenogram of a 21-year-old man with stage III Hodgkin's disease in whom shortness of breath and cough developed 24 hours after a bipedal lymphangiogram was done to assess the extent of involvement in retroperitoneal lymph nodes. This magnified view of the peripheral lung fields shows the granular pattern typical of this disorder.

TABLE 2.—*Drugs Associated With Pulmonary Vasculitis*

Foreign material injected intravenously	Sulfonamides
Nitrofurantoin	Hydralazine hydrochloride
Penicillins	Procainamide hydrochloride

likely a form of hypersensitivity pneumonitis, but pathologic studies have been infrequent and the results somewhat difficult to interpret.

Pulmonary Hypertension

Of all the drug-induced pulmonary disorders, pulmonary hypertension remains the least well understood. Experience in animal models, chance observations in patients and epidemiologic studies suggest that drugs can cause pulmonary hypertension. The lack, however, of a noninvasive method to measure pulmonary artery pressure has made study of the problem difficult.

In animal models, chronic pulmonary hypertension can be induced by oral administration of pyrrolizidine alkaloids such as monocrotaline. These substances are metabolized in the liver to a highly reactive pyrrolic derivative that binds irreversibly to lung, causing severe damage to lung blood vessels and the vascular pathology typical of pulmonary hypertension.[80,81] The herbicide paraquat can cause similar findings after ingestion by animals.[82] Although pyrrolizidine alkaloids and paraquat are not therapeutic agents, these observations have raised the possibility that the unexplained pulmonary hypertension seen in association with oral contraceptives[83,84] or the oral administration of the anorectic aminorex[85] might occur by similar mechanisms.

Sclerosis of esophageal varices with sodium morrhuate, a mixture of unsaturated fatty acids (including arachidonic acid) found in cod liver oil, has been reported as a cause of acute pulmonary hypertension and edema,[86] probably because the lungs are immediately downstream from varices and subject to damage. Intravenous injections in animals caused pulmonary hypertension and increased lung lymph flow, but no evidence for increased permeability of the lung capillary bed was found. The authors postulated that hypoalbuminemia may predispose patients with chronic liver disease to pulmonary edema in the presence of severe pulmonary hypertension induced by the sclerotherapy. Sodium morrhuate is cytotoxic to granulocytes, erythrocytes and endothelial cells in concentrations used clinically.[87] Similar changes of acute pulmonary hypertension and increased lung lymph flow are produced by intravenous injections of a fat emulsion (Intralipid) in animals[88] and can interfere with gas exchange in patients.[89] Prostaglandins may be involved as the effects of the fat emulsion on pulmonary hemodynamics can be blocked by indomethacin.[88]

Pulmonary Hemorrhage

Drug-induced pulmonary hemorrhage is a rare complication of anticoagulant therapy,[90] D-penicillamine,[91,92] moxalactam disodium[93] or ethiodized oil with radioactive iodine (Ethiodol-131).[71] Hemorrhage during heparin or warfarin sodium therapy suggests the presence of an intrapulmonary lesion[90] or a systemic predisposition to bleeding and presents as hemoptysis or, less frequently, as diffuse alveolar infiltrates and anemia. In the latter case, hemosiderin-laden macrophages are found in the sputum or bronchoalveolar lavage. D-Penicillamine-induced hemorrhage also presents as alveolar infiltrates and anemia, but also causes crescentic glomerulonephritis.[92,94] Moxalactam and ethiodized oil I 131 have been reported to cause spontaneous pulmonary hemorrhage in isolated case reports.

Summary and Directions for Future Research

A wide variety of drugs can cause damage to the lung vascular bed. The pulmonary predilection for vascular damage relates to a huge vascular surface area and blood flow—the largest among body organs. Clinical observations and animal models using drugs to damage the lungs have increased our understanding of these reactions. Recognition is critical to treatment because most of the reactions abate with drug withdrawal.

Although clinical observation will remain important in identifying and characterizing drug toxicity, future research will need to expand work with animals and in vitro techniques. Isolation and culture of lung vascular cells will allow study of cell biology, pharmacology and drug toxicity at the cellular level. Methods to isolate and culture vascular endothelial and smooth muscle cells are presently available and allow carefully controlled observation of pure cell populations. The use of these techniques to study the recognized mechanisms of drug vascular damage will greatly expand our present knowledge and doubtless will lead to the discovery of other, as yet unrecognized, mechanisms and possible therapeutic interventions.

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Intestinal Ischemia and Infarction Associated With Oral Contraceptives

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Thromboembolic vascular disease is a well-documented complication of oral contraceptive use. In all, 41 cases of mesenteric vascular ischemia or occlusion in women using oral birth control medications have been reported in the literature. "Reversible" ischemic enterocolitis or colitis (15 cases) and intestinal infarction (26 cases) represent the two clinical and pathologic presentations of this infrequently seen complication. Recovery is the rule in transient ischemia; clinically unmistakable intestinal necrosis carries a 31% mortality rate. Several pathophysiologic mechanisms, all unproved, have been proposed to explain these phenomena and the "hypercoagulable state." Recurrence is rare after the oral contraceptive regimen is discontinued.

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Oral contraceptives became available for use in the early 1960s. Since then, they have been prescribed for birth control, treatment of dysmenorrhea, menorrhagia, metromenorrhagia, endometriosis and suppression of postpartum lactation.[1] Their use peaked in the mid-1970s and has fallen slightly since, but it is estimated that more than 8 million American women and 50 million women worldwide are taking oral contraceptives.[1]

Not long after their introduction, however, adverse effects of oral contraceptives became known. The first report of a pulmonary embolus associated with the use of oral contraceptives was by Jordan in 1961[2] and was followed by several reports of superficial and deep vein thromboses, cerebrovascular accidents and myocardial infarctions in young women taking oral contraceptives. These alarming thromboembolic complications prompted several retrospective and prospective case-control and cohort studies that confirmed the increased risk of vascular events among oral contraceptive users. In a review of oral contraceptives and cardiovascular disease,[3] Stadel concluded that the relative risk among current users of oral contraceptives for idiopathic deep vein thrombosis or pulmonary embolus was 4 to 11 times, for myocardial infarction was 3 to 4 times and for stroke (thrombotic and hemorrhagic) was 5 times that of comparably aged women who never took birth control pills. Moreover, whereas smoking, increased age and estrogen content of the preparation appeared to increase these risks, the duration of oral contraceptive usage did not.

Although the numerous reports of complications of oral contraceptive use did not specifically address intra-abdominal vascular complications associated with them and therefore did not detail a definable risk of their occurrence, reports of more than 40 patients with small or large bowel (or both) ischemia or infarction have been published. The first such report in 1963 by Reed and Coon[4] was of the case of a 37-year-old woman, using oral contraceptives for two months, who had acute abdominal pain and at laparotomy was found to have gangrenous small bowel together with superior mesenteric vein occlusion with thrombus; she died postoperatively.

The exact incidence of thrombotic events of the abdominal vasculature has not been determined, as the information available has been presented as case reports from Europe and the United States and has not been subjected to vigorous cohort studies. Overall, 41 cases of "reversible" ischemic colitis or enterocolitis or of clinically unmistakable infarction have been reported in association with oral contraceptive usage.[4-25] These two broad clinical and pathologic categories can be subdivided according to distribution along major vascular trunks (celiac, superior mesenteric, inferior mesenteric) and according to the site of thrombus in either the arterial or the venous system (Table 1).

"Reversible" Ischemic Colitis or Enterocolitis

Of the 41 patients whose cases were reviewed, 15 (37%) presented with "reversible" ischemic colitis or enterocolitis. The clinical presentation was in all instances abdominal pain,

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TABLE 1.—*Clinical Presentation and Distribution of Vascular Lesions (N = 41)*

Presentation	*Vascular Distribution or Site of Thrombus*	*Patients, Number*	*Deaths, Number*	*Repeat Laparotomy, Number*
"Reversible" enterocolitis (N = 15)	Superior mesenteric	10	0	. . .
	"Watershed zone"	2	0	. . .
	Inferior mesenteric	3	0	. . .
Bowel infarction (N = 26)	Celiac artery	2	1	1
	Superior mesenteric artery	6	2	2
	Superior mesenteric vein	17	6	6
	Inferior mesenteric artery	1	0	0
	Inferior mesenteric vein	. . .	. . .	. . .

ABBREVIATIONS USED IN TEXT

HDL = high-density lipoprotein
SMA = superior mesenteric artery
SMV = superior mesenteric vein

usually colicky in nature, lasting from hours to weeks and associated with bloody diarrhea or gross hematochezia in 13 of 15 patients (87%). Nausea and vomiting were less consistently reported (5/15 or 33%). Fever, although not always present on admission, was reported at some time during the initial hospital stay in only a third of patients (5/15). Changes in stool caliber, anorexia and weight loss were not noted in the reports.

Evaluation of these patients was predominantly noninvasive. Leukocyte counts, described in only ten patients, were elevated (> 10,000 per μl) in all, and this was the only laboratory study with consistently abnormal results. Serum amylase levels were normal when reported. Plain radiographs of the abdomen were normal in most patients in whom these were done, although occasional reports of nonspecific large or small bowel ileus or bowel wall thickening were mentioned. Overall, barium contrast radiography was the most helpful diagnostic tool. Either the barium enema or upper gastrointestinal series with small bowel follow-through examination was abnormal in all 15 patients. Findings consisted of narrowed, spastic areas of colon or terminal ileum on barium enema examinations (Figure 1). The lesions were generally continuous but segmental in nature—that is, no skip lesions characteristic of Crohn's disease were observed. The mucosa was irregular and often ulcerated or spiculated. Characteristic "thumbprinting" was seen in 75% (6/8) of abnormal barium enemas. This finding, although not specific for intestinal ischemia, is thought to represent submucosal edema or hemorrhage, both of which are common pathologic changes in this disorder (Figure 2).

The three patients with abnormal small bowel barium radiographs had wall thickening, stenosis and rigidity with proximal dilation. The ileum was involved in all patients. "Thumbprinting" of the mucosa was seen in only one of these patients; no superficial mucosal irregularities were described.

Sigmoidoscopic and colonoscopic visualization of the involved areas added little to the diagnostic evaluation of these patients with "reversible" ischemic colitis or enterocolitis. Mucosal changes of friability, erythema and ulceration and luminal narrowing and spasm were encountered in some patients. Biopsy findings, when reported, were either normal or showed only nonspecific inflammatory changes. One could speculate about the potential usefulness of endoscopic biopsies for (1) noting rectal involvement, which would likely exclude ischemia as an etiologic factor, (2) discovering crypt abscesses or granulomas that could be suggestive of inflammatory bowel disease, (3) collecting mucosal biopsy specimens or exudate for culture to exclude infectious causes (tuberculosis, lymphogranuloma venereum, *Campylobacter* or *Yersinia*) or (4) diagnosing neoplasia. It appears, however,

Figure 1.—Barium enema shows a focal stricture in the descending colon.

that these endoscopic studies did not obviate the need for barium examinations in these patients.

Three patients underwent laparotomy for diagnosis and treatment. We reported the case of a patient with a descending colon stricture from colitis that was resected for relief of pain and hematochezia and to confirm histologically the absence of carcinoma in the stricture, which could not be fully evaluated colonoscopically (Figure 3).[5] Of note, multiple thrombi in the branches of the inferior mesenteric artery were detected on microscopy. Similarly, Egger and Mangold described the case of a woman with a large bowel obstruction due to an inflammatory mass replacing the normal configuration of the distal transverse colon, splenic flexure and proximal descending colon.[6] A transverse colostomy was done without bowel resection. Gross pathologic examination of the vascular tree showed no abnormalities; the patient recovered and a follow-up barium enema three months later was normal. The third patient also was explored because of abdominal pain and hematochezia—at laparotomy an edematous ascending colon and normal mesenteric vessels were found.[7] No colotomy was done and she did well postoperatively.

The course of these 15 patients with reversible ischemic colitis or enterocolitis was one of gradual improvement while receiving supportive treatment within days to weeks after diagnosis and discontinuation of the oral contraceptive regimen. No patient was reported to have a recrudescence or reappearance of symptoms after the initial hospital admission and elimination of oral contraceptives. Indeed, these clinical observations were further corroborated in follow-up barium radiographs. Of the 11 patients with initially abnormal barium enemas as described above, 10 had repeat examinations from five to eight months later—9 were normal and 1 showed narrowing of the splenic flexure. The three previously abnormal small bowel barium radiograph examinations were all normal when repeated seven days to seven weeks later. None of these patients died of their illness.

The anatomic distribution of the abnormalities in ischemic colitis or enterocolitis can best be evaluated with respect to the large vessels serving the involved regions. Unfortunately, few pathologic specimens were provided in this less-seriously ill group. Two thirds of the patients had radiographic changes in the superior mesenteric artery distribution from the ligament of Treitz to the distal transverse colon, with a predominance of lesions in the terminal ileum and proximal half of the colon. Although the findings of neither arteriographic nor pathologic examinations are available that could confirm embolic disease, the predominance of abnormalities in this distribution and the wide luminal diameter and obliquity of the angle of the superior mesenteric artery at its origin from the aorta make this cause most likely.[26] Two patients had involvement in the "watershed zone" of the superior mesenteric and inferior mesenteric arterial distributions (distal transverse and proximal descending colon), and three patients had de-

Figure 2.—Barium enema depicts "thumbprinting" of the ascending colon in ischemic colitis. The scalloped margins represent submucosal hemorrhage and edema, separated by haustral folds.

Figure 3.—Barium enema with persistent descending colon stricture and mucosal irregularity. Segmental resection of this region disclosed occluding arterial thrombi and focal colitis but no malignancy.

scending colon (inferior mesenteric) abnormalities. In one patient, arterial thrombi were discovered in a resected specimen.[5] As expected from the dual vascular supply of the rectum, no ischemia occurred here.

Bowel Infarction Among Users of Oral Contraceptives

There are case reports of 26 women using oral contraceptives who had documented bowel infarction. These women were obviously more seriously ill; in fact, 8 of 26 (31%) died of the vascular disease or postoperative complications. Vascular occlusion with thrombus of the branches of all three major distributions was documented, but disease location was skewed toward that of the superior mesenteric artery (SMA) and vein (SMV)—6 of 26 (23%) had disease in the SMA, 17 of 26 (65%) in the SMV. Two patients had vascular occlusion in celiac, superior mesenteric and inferior mesenteric arteries, one in both the SMV and inferior mesenteric vein, but the remainder showed only one trunk supply compromised.

As with reversible ischemia, abdominal pain was the presenting symptom in all of these patients. Crampy in nature, the pain had been present for up to 18 months before admission to hospital but, in general, symptoms prompting medical attention were of less than two weeks' duration in 24/25 (96%) for whom the information was provided; 19/25 (76%) had pain for less than one week and 7/25 (28%) had pain for less than 24 hours.

For patients with more prolonged pain, usually an exacerbation of the discomfort, the onset of vomiting (nine patients), diarrhea (three patients), hematochezia (two patients) or hematemesis (two patients) occasioned admission to hospital. Peritoneal signs, fever and hypotension were inconsistently reported. One patient with an abdominal bruit was noted.

As with reversible ischemia, leukocytosis and a normal serum amylase level were present in all but one patient for whom data were presented. Due to the acuteness of illness, radiographic evaluation was limited and, with the exception of free air on upright plain abdominal radiographs in two of four patients and barium enema evidence of splenic flexure and descending colon narrowing with "thumbprinting" in one of three done, was not helpful in diagnosis.

Of the 26 patients with bowel infarction, 25 underwent laparotomy for diagnosis, treatment or both. In all but three, resection was required of gangrenous, dusky, pale or edematous small or large intestine (or both) of varying lengths. Free peritoneal fluid or fecal contamination was infrequently reported. Thrombi occluding one or several lumina of arterial or venous structures were found in all patients, either grossly at laparotomy (eight patients) or following pathologic examination. A single patient showed necrotizing vasculitis of a branch of the inferior mesenteric artery without clot detected.[7] A 15-cm dark, indurated segment of descending colon was resected. A follow-up barium enema 17 days after the operation did not show any further evidence of ischemia.

The three patients in whom no resection was carried out are of special interest.[9,10] One patient with suspected intestinal infarction had multiple, nodular mesenteric venous occlusions but viable bowel. In a second patient, a thrombus occluding the SMA distal to the origin of the middle colic artery was removed and a previously pale section of small bowel regained normal color. The patient did well thereafter. A third woman undergoing laparotomy had edematous but viable small bowel with normal peristalsis. A thrill was felt at the celiac artery. No resection was done. Ten days later a recurrence of symptoms prompted reexploration, which disclosed gangrenous bowel from mid-small bowel to mid-ascending colon.

A second laparotomy was not uncommon. In fact, 11 of 26 (42%) required at least one additional exploration for further resection or repair of fecal fistulas. The findings of two "second-look" operations were unremarkable.

With two exceptions, both of whom had documented arterial occlusion of branches of all three major vascular trunks, recurrent ischemia or necrosis did not develop in any patient after oral contraceptive use was discontinued.[11]

In summary, therefore, two clinical presentations of ischemic bowel disease were noted among the overall group of 41 patients. All 41 women took birth control pills for varying durations—from 10 days to 10 years, with a mean of 2.2 years. The length of contraceptive use did not correlate with the severity of disease, presence of "reversibility" or mortality. These findings are consistent with data regarding other thromboembolic phenomena associated with oral contraceptive use.[3]

Pathogenesis of "Reversible" Ischemia

Can we incriminate the oral contraceptive drug as causative in these cases? Risk factors for intestinal ischemia such as polycythemia vera, the nephrotic syndrome, portal hypertension, atherosclerosis, surgical trauma and vasculitis were, with the exception of one case,[7] absent. "Spontaneous" ischemic colitis has been reported in young adults by Miller and co-workers[27] and Clark and associates.[28] Review of the combined data from these studies shows that 71% of the women in whom spontaneous ischemic colitis developed were using oral contraceptives at the time of diagnosis. Of note, one of the women not using the birth control pill was six months' pregnant, suggesting an endogenous elevation of estrogen and progestin levels as the cause of the ischemia.

It has been argued that the reversible colitis observed may not indeed represent ischemia.[29] The small number of cases necessitating resection and histopathologic confirmation of ischemia or thrombosis and the lack of angiographic evidence constitute the main objections. Indeed, the need for resection is unusual, with residual stricture and obstruction and uncertainty regarding the presence of neoplasm being the main indications. In this series, only one patient[5] required colonic resection for an ischemic stricture, and arterial thrombi were found in the specimen. Angiography, rarely used in this series, is a disappointing diagnostic tool,[30] as the main trunks are usually normal and the small marginal vessels, the most likely to be involved, are poorly seen. In older age groups, where atherosclerotic changes are to be expected, angiographic abnormalities are more frequently seen, but are less specific. The most useful evidence for an ischemic process appears to be the normalization of the barium enema changes of luminal narrowing, mucosal irregularities and thumbprinting,[31] occurring in 91% of patients.

Pathogenesis of Oral Contraceptive-Induced Intestinal Infarction

The issue is clearly much less controversial in the group of patients showing documented intestinal necrosis. Both venous

and arterial occlusions in major trunks and smaller vessels have been easily documented. The age of the patients involved and lack of preexisting risk factors make oral contraceptive use the likely cause.

The pathophysiology of oral contraceptive-induced ischemia and infarction is controversial and likely multifactorial (Table 2). In general, it is known that the highest incidence of thrombotic complications occurred when doses of estrogens and progestins were used far in excess of those needed for birth control.[32] When estrogen dosages in contraceptives were decreased by 50%, the reported incidence of venous complications fell from 25.9 to 7.2 per 100,000 users of oral contraception.[33] Arterial disease remained unchanged, but it appears that progestins are more implicated in arterial occlusion and estrogens in venous occlusion.[34,35]

In numerous articles, the effects of oral contraceptive agents on the clotting system have been evaluated. In general, the results are not uniform and in many cases are contradictory. Consistently, however, platelet count, prothrombin time and partial thromboplastin times are unchanged.

Platelet production of thromboxane A_2 has been reported to be increased,[36] and platelet aggregation seems less inhibited by endothelial cells[37] in oral contraceptives users. In a study in rabbits, no change was found in platelet aggregation in animals receiving both estrogens and progestins, which was attributed to an offsetting reduction in prostacyclin inhibition by the progestin component.[38]

Estrogens increase hepatic production of coagulation factors. Consistently, factor VII level and activity have been noted to be elevated in oral contraceptive users compared with those in controls.[38,40] Whether these elevations correlate with a "hypercoagulable state," however, is unclear since normally clotting factors circulating in the plasma are in greater concentrations than are needed for hemostasis.

Levels of antithrombin III, a protein that inhibits conversion of prothrombin to thrombin, have been reported to be normal or depressed in quantitative and functional analyses in oral contraceptive users. Differences in measuring techniques and individual variability have accounted for discrepant results. Still, when concentrations were depressed, they rarely reached the 40% to 55% levels considered to be associated with spontaneous coagulation.[41] Additionally, plasminogen activator levels were lower in some oral contraceptive users, correlating with depressed fibrinolysis and venous, but not arterial, thrombosis.[42] Thus, the clotting cascade and fibrinolytic system, especially elevated factor VII levels, depressed levels of antithrombin III and diminished fibrinolysis, *may* play supporting roles in the so-called hypercoagulable state.

The role of lipids and lipoproteins has also been noted.[34,39,43] Serum triglyceride levels are mildly but consistently elevated in oral contraceptives users, whereas total cholesterol levels are not. Levels of very-low-density lipoprotein and low-density lipoprotein, the latter clearly linked to the incidence of cardiovascular disease, appear increased, and levels of high-density lipoprotein (HDL), the "protective" lipoprotein, vary, depending on the hormonal concentration of the particular birth control pill. Substantial evidence exists that estrogens increase the HDL levels and progestins depress them.

Finally, only a small body of literature describes vascular wall changes in patients receiving hormonal agents. Danforth and colleagues described changes of vascular smooth muscle hyperplasia, fragmentation of the reticulum network and attenuation of the elastic tissue in rabbits administered norethynodrel and mestranol.[44] Irey and co-workers documented intimal endothelial proliferation, subendothelial fibrosis and luminal narrowing, with or without occluding thrombus, in a small number of women (20%) who died of thromboembolic disease while using an oral contraceptive[45]; these findings were not observed in a control population of women not using oral birth control medications but with fatal thromboembolic disease. They postulated there was primary endothelial damage with subsequent vascular changes and occlusion with thrombus. In the series presented here, perivascular fibrosis was seen in two patients with gangrenous small bowel.[16]

TABLE 2.—*Proposed Mechanisms of Ischemia/Infarction*

Increased	*Decreased*
Platelet aggregation	Antithrombin III level
Factor VII level and activity	Plasminogen activator level
Triglyceride level	HDL (progestins)
VLDL, LDL	

HOL = high-density lipoprotein, LOL = low-density lipoprotein, VLDL = very-low-density lipoprotein

Therefore, despite the extensive number of articles recording possible mechanisms, precisely how oral contraceptives induce an array of ischemic and necrotic intestinal changes has not been defined. The most likely explanation is a multifactorial set of conditions (increased clotting factors, altered platelet aggregation and adhesiveness, diminished fibrinolysis, elevated circulating lipoproteins and possibly primary vascular endothelial damage) that favors vascular narrowing or occlusion.

Conclusion

There appears to be a finite, although poorly quantitated, risk of vascular occlusive disease in women using oral contraceptives. Reversible small or large bowel ischemia and frank intestinal necrosis represent the two subtypes that have been described. The latter disorder carries a high mortality rate (31%). The pathophysiology is unclear and is likely complex and multifactorial. Fortunately, discontinuing oral contraceptive use seems to virtually eliminate the risk. Although the incidence of these intra-abdominal vascular complications, based on their reporting in the medical literature, seems to be decreasing concomitant with the lowering of estrogen dose, sporadic cases continue to occur. A clinician must therefore be attentive to early abdominal symptoms in women taking oral contraceptives and prescribe those preparations with the lowest hormone dosages consistent with birth control, but without breakthrough bleeding.

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Clinicopathologic Conference

Malignant Hypertension and Asymmetric Septal Hypertrophy in a 43-Year-Old Black Man

Discussants

JOHN C. RUTLEDGE, MD, *and* ALVIN ENG, MD

Moderator

JOSEPH SILVA, Jr, MD

JOSEPH SILVA, JR, MD:* *Discovering the cause of hypertension in any given patient may be confounding to a clinician. The diagnostic evaluation can be simple and inexpensive, or labor-intensive and costly. The evaluation is sometimes not as rigorous as that used for other illnesses. This shortcoming is related in part to the cause of hypertension being relegated to the categories of either essential or renovascular. The patient discussed here was selected because the results of the history and physical examination show that these elements may provide clues in the workup of these patients. In addition, important clinical deductions can be made from preliminary laboratory data to better characterize the cause of hypertension. Dr John Rutledge is Director of the Hypertension Clinic at the University of California Davis Medical Center and will discuss this case. Dr Eng will present the case.*

Case Presentation

ALVIN ENG, MD:† The patient is a 43-year-old black man with a one-year history of hypertension and glucose intolerance treated with hydrochlorothiazide and triamterene (Dyazide) and oral hypoglycemic agents. Two days before admission his regimen was changed to insulin. While at work, he noted a severe occipital headache unrelieved by acetaminophen. He had had no alterations in mental state, dizziness, visual changes, paralysis, weakness or paresthesias. He left work early and went to bed. He was found the next morning by his fiancée to be extremely lethargic, confused and dysarthric and was brought to the emergency room where he was given an infusion of 50% glucose solution, thiamine and naloxone, without effect. No history of recent illnesses, alcohol abuse, smoking or intravenous drug abuse was obtained. Present medications were Dyazide, one tablet twice a day, and insulin.

On physical examination he was awake but lethargic and offered no complaints. His temperature was 34.4°C (94°F) and blood pressure was 166/104 mm of mercury. Heart rate and respiratory rate were 64 and 12 per minute, respectively. Examination of the head, eyes, ears, nose and throat showed no abnormalities. The skin showed no abnormalities. The lungs were normal to auscultation and percussion. On cardiovascular examination there were no murmurs, gallops, rubs or clicks. The abdomen was nontender and without organomegaly. Pulses were equal and brisk. Neurologic examination revealed no focal or lateralizing signs.

Laboratory examination elicited the following: hemoglobin 15.6 grams per dl, leukocyte count 7,100 per μl. Serum chemistry values were sodium 133, potassium 3.1, chloride 96 and carbon dioxide 28 mEq per liter; creatinine 0.8, glucose 160 and calcium 9.5 mg per dl. A chest roentgenogram was unremarkable. An electrocardiogram showed a sinus rhythm, a rate of 60, axis +45 degrees, normal intervals and a probable U wave (Figure 1). Urinalysis showed a specific gravity of 1.006, pH 6.0 and 0 to 2 leukocytes per high powered field. Serum and urine toxicology screens were negative.

Hospital Course

The patient was admitted to the medical intensive care unit for evaluation of hypothermia. His blood pessure on arriving at the unit was 260/160 mm of mercury with a sinus tachycardia of 150 beats per minute. A new grade 3/6 crescendo-decrescendo systolic murmur was now audible at the apex and

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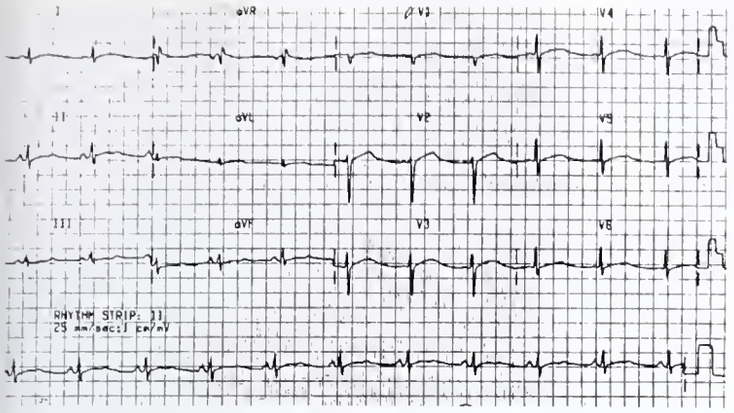

Figure 1.—A 12-lead electrocardiogram shows U waves in leads II, III, aV_F and V_{4-6}.

radiated throughout the precordium and neck. The murmur increased during Valsalva's maneuver and diminished with isometric exercise and squatting. An echocardiogram showed normal valves and wall motion, but systolic anterior motion of the mitral valve was present. Left ventricular dimensions were as follows: left ventricular end-diastolic diameter 4.1 cm (normal 3.5 to 5.7), interventricular septum 2.8 cm (normal 0.6 to 1.1) and posterior wall thickness 1.5 cm (normal 0.6 to 1.1).

Three doses of hydralazine hydrochloride, 10 mg, were given intramuscularly without effect. A sodium nitroprusside infusion and propranolol hydrochloride, 20 mg by mouth, did not cause a significant reduction in blood pressure. Administering verapamil, 5 mg intravenously, resulted in hypotension (70/40 mm of mercury). The blood pressure stabilized at 150/90 mm of mercury after fluid resuscitation and 15 minutes later rose to 240/130 mm of mercury. Sodium nitroprusside was titrated up to 6 μg per kg per minute with gradual lowering of the blood pressure to 140/70 mm of mercury. A total of 1.5 mg digoxin was given intravenously to reduce the heart rate to 90 to 110 beats per minute. Because of the presence of asymmetric septal hypertrophy, metoprolol tartrate, 5 mg, was given intravenously with elevation of the blood pressure to 220/140 mm of mercury and the sodium nitroprusside dosage was again increased to lower the blood pressure.

Further diagnostic studies were initiated.

Discussion

JOHN C. RUTLEDGE, MD:* To summarize the salient features of this case, the patient is a middle-aged black man with a one-year history of hypertension and diabetes mellitus with a recent change in therapy from an oral hypoglycemic agent to insulin. A severe occipital headache developed that was followed by lethargy, confusion and dysarthria. The results of a physical examination on admission were significant for hypothermia, a mildly elevated blood pressure and a heart rate of 64 beats per minute. Laboratory studies revealed hyponatremia and hypokalemia, and the electrocardiogram showed prominent U waves. A dilute urine was noted by urinalysis. During the hospital course he had paroxysms of hypertension and hypotension. Clinical and laboratory evidence of cardiac asymmetric septal hypertrophy was present.

This case presents a multitude of the clinical problems that are commonly encountered in the care of hypertensive patients, such as hypokalemia, acute neurologic events and paroxysmal hypertension. I will first discuss some of the pathophysiologic mechanisms that may be operating in this case, which will be followed by a discussion of the differential diagnosis. Finally, I will comment on some unanswered questions and make concluding remarks.

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Paroxysmal Hypertension

The most striking feature of this case is the paroxysms of severe hypertension. One would surmise that the patient's hypertension is of relatively recent onset given the lack of signs of end-organ damage. The most common causes of paroxysmal hypertension in this setting are an excess of endogenous catecholamines and of exogenous sympathomimetic agents.[1] Included among the possible causes are pheochromocytoma, acute pulmonary edema, acute myocardial infarction, stroke, brain tumor, rebound hypertension after cessation of antihypertensive medication, hypertensive crisis associated with monoamine oxidase inhibitors, intake of sympathomimetic drugs and autonomic dysreflexia (quadriplegia). Excess catecholamines are especially likely in this case given the patient's tachycardia during the paroxysm of hypertension.

Acute Neurologic Event Associated With Hypertension

The patient's symptoms on presentation were headache with progression to confusion, lethargy and dysarthria. On physical examination there were no lateralizing signs. The differential diagnosis in this setting includes intoxications, metabolic disturbances such as hypoglycemia and hyponatremia, systemic infection, endocrine abnormalities such as thyrotoxicosis, circulatory collapse from a variety of causes, seizure, hyperthermia or hypothermia, concussion, hypertensive encephalopathy and a subarachnoid hemorrhage. Systemic infection, circulatory collapse and concussion are not suggested by this patient's clinical presentation. Intoxications, metabolic disturbances, endocrinologic causes and hypothermia will be considered later.

This patient's presentation suggests a ruptured saccular aneurysm. Defects in the arterial media and elastica are responsible for aneurysmal dilatation, which usually occurs in arteries comprising the circle of Willis or its branches. A ruptured saccular aneurysm may present in several ways, and certainly this patient's presentation of a severe headache followed by partial or complete loss of consciousness without lateralizing signs is consistent with this diagnosis. Nuchal rigidity, subhyaloid hemorrhages of the retinal vessels and bilateral Babinski's signs are absent, however. Patients with congenital polycystic disease of the kidney and coarctation of the aorta have an increased incidence of saccular aneurysms. Computed tomography (CT) and examination of the cerebrospinal fluid are helpful in making a diagnosis.

In a patient such as this with paroxysms of hypertension, hypertensive encephalopathy is certainly a consideration. This syndrome commonly presents with headache as the initial complaint, followed by lethargy, stupor, coma, seizures, visual impairment, nausea and vomiting. MacKenzie and colleagues have evaluated the effect of acute changes in arterial blood pressure on cerebral blood flow in cats.[2] These studies show that there is an autoregulatory phenomenon governing cerebral blood flow. As arterial pressure is reduced, progres-

sive dilation of the cerebral blood vessels occurs and, as flow through the cerebral vessels increases, vasoconstriction ensues. When the mean arterial pressure reaches 180 mm of mercury, however, the vessels dilate with consequent increased cerebral flow and hyperperfusion of the brain. Cerebral edema follows with resultant hypertensive encephalopathy. Patients with chronic hypertension who have structural thickening of the vasculature appear to be more resistant to this failure of autoregulation than patients with a normal blood pressure. Any primary or secondary causes of hypertension can result in malignant hypertension with hypertensive encephalopathy. The most common cause of hypertensive encephalopathy is essential hypertension, which occurs in more than 90% of the hypertensive population. Of the secondary causes of hypertension, encephalopathy is more commonly seen with acute glomerulonephritis, toxemia of pregnancy, the use of monoamine oxidase inhibitors following ingestion of tyramine, the use of sympathomimetic drugs, renovascular hypertension and pheochromocytoma.[3]

Hypertension and Hypokalemia

In about 10% of patients who take thiazide diuretics for hypertension, hypokalemia will develop.[4] The overwhelming majority of patients with hypertension who have hypokalemia are on thiazide diuretic therapy. Half of hypertensive patients with hypokalemia that is unprovoked by thiazide diuretics will have primary aldosteronism.[5(p300)] Other conditions in which hypokalemia and hypertension are associated include diarrhea, estrogen therapy, renovascular hypertension, accelerated or malignant hypertension, salt-wasting renal disease, licorice ingestion and excess mineralocorticoids.

Dyazide (Smith Kline & French) is a capsule composed of 25 mg of hydrochlorothiazide and 50 mg of triamterene. Although the problem of hypokalemia is reduced because triamterene is a potassium-sparing diuretic, hypokalemia is still seen and often in combination with hyponatremia. The hypokalemia induced by accelerated or malignant hypertension is felt to be due to renal ischemia with activation of the renin-angiotensin-aldosterone system.[6] Hypokalemia as a result of primary aldosteronism will be discussed later.

U Waves

The U wave follows the T wave on the electrocardiogram and usually is positive in leads in which the QRS complex is positive. The mechanism that results in a U wave is uncertain but may be a result of afterpotentials at the beginning of diastole[7] or repolarization of the Purkinje system.[8] Abnormalities of the U wave include increased voltage, U waves in leads where they are not normally seen or inversion of U waves. Hypokalemia[9] and hypothermia[10(p80)] increase the U-wave amplitude. A negative U wave is reported to be highly specific for the presence of heart disease and is associated with other electrocardiographic abnormalities in more than 90% of patients.[11]

Asymmetric Septal Hypertrophy

Asymmetric septal hypertrophy is classified under the broader heading of hypertrophic cardiomyopathy. This syndrome is characterized by asymmetric septal hypertrophy (septum to posterior wall thickness ratio of 1.3/1.0), dynamic left ventricular outflow obstruction and diastolic dysfunction.

The dynamic outflow obstruction produced with asymmetric septal hypertrophy may be the result of systolic anterior motion of the mitral leaflets and chordae tendinae, large papillary muscles or abnormal shape and reduced size of the left ventricular cavity in systole.[12] Systolic anterior motion of the mitral valve occurs with ventricular ejection when a high-velocity jet pulls the mitral valve apparatus into the left ventricular outflow tract by a Venturi effect. A crescendo-decrescendo systolic murmur and a dynamic left ventricular outflow tract gradient are produced. The dynamic obstruction can be worsened by increased left ventricular contractility, reduced left ventricular volume (preload) and decreased aortic impedance (afterload). Valsalva's maneuver or standing erect reduces the ventricular volume and increases the intensity of the murmur. In contrast, squatting (which increases ventricular volume and afterload) and isometric exercise (which increases afterload) decrease the dynamic obstruction and the intensity of the murmur. The diastolic dysfunction associated with asymmetric septal hypertrophy is the result of decreased compliance of the left ventricle. This elevates ventricular pressures, which in turn causes pulmonary congestion and the most common symptom of hypertrophic cardiomyopathy, breathlessness.[13]

Hypertrophic cardiomyopathy has been found in association with lentiginosis (the diffuse presence of multiple small dark brown macules) and other disorders of neural crest tissue including pheochromocytoma.[14(p1310)] A similar hemodynamic pattern has been found in infants of diabetic mothers[15] and in patients with Friedreich's ataxia.[16] In addition, aberrant catecholamine function in a developing embryo heart has been implicated in the abnormal orientation of myofibrils seen in hypertrophic cardiomyopathy.[17]

Differential Diagnosis

Although essential hypertension is the most common cause of accelerated or malignant hypertension, this patient's paroxysms of hypertension are not consistent with this diagnosis. Likewise, this patient's presentation makes chronic renal disease, coarctation of the aorta and, especially, oral contraceptive-induced hypertension unlikely.

Renovascular Hypertension

In a recent study approximately 1% of adults with hypertension were found to have functionally significant renovascular disease.[18] When a group of patients with surgically cured renovascular disease was compared with a carefully matched group with essential hypertension, the presence of an abdominal bruit was the only clear discriminator.[19] The bruit was heard over the flank in 12% of patients with renovascular hypertension compared with 1% of patients with essential hypertension. Bruits in the epigastrium usually reflected stenosis of the celiac artery. A high-pitched systolic and diastolic abdominal murmur radiating laterally is strong evidence of significant renal artery stenosis. Patients with renovascular hypertension tend to have a shorter duration of hypertension and are usually 50 years of age or older. In addition, grade 3 or 4 funduscopic changes, a blood urea nitrogen level greater than 20 mg per dl and hypokalemia tend to be more common in patients with renovascular hypertension.

Several features of this case do not suggest renovascular hypertension. This patient was black and persons of this race have a low incidence of renovascular hypertension.[19] No bruit or funduscopic changes were noted, and paroxysmal hypertension is not characteristic of this disease.

Cushing's Syndrome

This syndrome is caused by an excess of glucocorticoids. Hypertension is present in 80%[20] and may be severe, with diastolic blood pressures greater than 130 mm of mercury.[21] Hypertension may be the result of the salt-retaining action of high levels of glucocorticoid,[22(p714)] increased production of mineralocorticoids usually seen with adrenal tumors or ectopic adrenocorticotropic hormone tumors,[23] increased levels and activity of renin-angiotensin[24] and increased vascular reactivity to pressor substances.[25] Clinical features helpful in the diagnosis of Cushing's syndrome are osteoporosis by x-ray film, central obesity, generalized obesity, proximal muscle weakness (knee bend), plethora, ecchymoses and hypokalemia.[26] The presence of striae, hypertension, edema, hirsutism, oligomenorrhea and an abnormal glucose tolerance test are of little discriminatory value. Given the patient's clinical presentation, I feel the diagnosis of Cushing's syndrome is unlikely.

Primary Aldosteronism

The clinical expression of primary aldosteronism can be related to volume expansion and hypokalemia. Hypertension in this syndrome may be severe,[27] and in one report it was suggested that a high proportion of patients with malignant hypertension have primary aldosteronism.[28]

Mineralocorticoid excess causes increased reabsorption of sodium and water and leads to volume expansion. In contrast to pathophysiologic disorders accompanying secondary aldosteronism, edema is notably absent in primary aldosteronism. The headache noted in primary aldosteronism, which is more severe, frequent and persistent than in essential hypertension, has been attributed to volume expansion. It is generally frontal rather than occipital and tends to occur in the early morning hours.

At presentation most patients have hypokalemia, but in one series as many as 22% had a normal serum potassium level.[29] Aldosterone exerts its effects in the distal tubule and collecting duct. The escape from volume expansion in primary aldosteronism involves a lesser degree of sodium reabsorption in the proximal tubule and increased sodium reabsorption in exchange for potassium in the distal tubule. There is also an exchange of sodium for hydrogen ion so that metabolic alkalosis is generated with increased proximal and distal reabsorption of bicarbonate. The clinical consequences of hypokalemia include weakness, paralysis, metabolic alkalosis, glucose intolerance and polyuria. In addition, most patients with primary aldosteronism will manifest a serum sodium level of 140 mEq per liter or greater.

A number of characteristic features of primary aldosteronism are present in this patient—that is, hypokalemia, the usual age range (30 to 50 years of age), glucose intolerance and accelerated or malignant hypertension. The patient did not have normal or increased serum sodium levels (he was receiving a diuretic, however), metabolic alkalosis, weakness and polyuria. Also, paroxysmal hypertension and tachycardia are not typical of primary aldosteronism.

Brain Tumor

A review of the literature by Bell and Doig shows 27 reported cases of paroxysmal hypertension associated with an intracranial tumor.[30] Hypothalamic compression due to suprasellar extension of pituitary chromophobe adenomata can cause striking changes in heart rate and blood pressure. Clinical features of brain tumors suggestive of pheochromocytoma were headache, tachycardia, excessive sweating, anxiety, tremor, nausea and vomiting. Localizing neurologic signs were initially absent in 5 of 27 patients, cerebrospinal fluid pressure was elevated in 73% and hypothermia occurred in one patient. Three patients had increased urinary catecholamine levels.

This patient's presentation is consistent with a brain tumor as the cause of paroxysmal elevation of blood pressure, but one would expect some premonitory symptoms and signs, papilledema or localizing neurologic signs in most patients presenting with this diagnosis. Also, we presume the patient's sensorium and body temperature must have improved during the hospital stay; otherwise, he could not have done Valsalva's, handgrip and squatting maneuvers. This implies a transitory nature to the altered state of consciousness, which would be uncommon with an intracranial tumor.

Pheochromocytoma

Pheochromocytoma can be asymptomatic or present with dramatic symptoms and signs. Commonly encountered symptoms and signs include hypertension, which may be sustained, paroxysmal or both; headache; sweating; palpitations with tachycardia or arrhythmias; weight loss; pallor; nausea; tremor; anxiety, and abdominal discomfort. The type of catecholamine that is predominantly secreted to a large extent determines the symptoms and signs.[31] Predominantly norepinephrine-secreting tumors are associated with symptoms of α-adrenergic stimulation: systolic and diastolic hypertension and reflex bradycardia. In the rare epinephrine-secreting tumors, β-adrenergic stimulation is more common: systolic hypertension, hyperglycemia, anxiety, shortness of breath and sometimes even periods of hypotension. In the very rare dopamine-secreting tumors, the presentation is one of a normal blood pressure or hypotension, tachycardia, diarrhea, polyuria and nausea. Most pheochromocytomas predominantly secrete norepinephrine with lesser contributions of epinephrine and dopamine.

Certain features of this case are in keeping with the diagnosis of pheochromocytoma. Both hyperglycemia and hypoglycemia are associated with catecholamine-secreting tumors. Neurologic events as a result of paroxysms of hypertension are common and include nonfocal disorders such as hypertensive encephalopathy, seizures and subarachnoid hemorrhage. Asymmetric septal hypertrophy is associated with pheochromocytoma. Paroxysms of hypertension are characteristic of catecholamine-secreting tumors. Likewise, hypotension is commonly noted with pheochromocytomas, but in this case hypotension may be related to a contracted intravascular volume and the use of verapamil with its potent vasodilating and negative inotropic properties. In addition, the response to β-adrenergic blocking agents like metoprolol, which allows unopposed α-adrenergic stimulation and exacerbation of hypertension, is characteristic of pheochromocytoma. The use of digoxin for the treatment of the patient's

rapid heart rate probably represents treatment of a paroxysmal supraventricular tachycardia (such as atrial fibrillation), which is also frequently noted with catecholamine-secreting tumors. Lest we become too confident of the diagnosis of pheochromocytoma, however, the literature shows us that only 50% of patients suspected of having pheochromocytomas actually have the disease.

In this patient, symptoms typical of pheochromocytoma that are absent include sweating, weight loss, pallor, nausea, tremor, anxiety and abdominal discomfort. Also, hypothermia cannot be explained by pheochromocytoma alone. A recent review of the causes of hypothermia lists a diverse group of diseases.[32] Included in this list are brain tumor, seizure and hypoglycemia, all of which are possibilities in this patient. I suspect, however, that the patient's altered sensorium was a result of hypertensive encephalopathy with or without a seizure that resulted in aberrations of thermoregulation and the hypothermia observed.

Other Causes of Hypertension

A large number of other possible causes of hypertension has been described. These include congenital adrenal hyperplasia (C-11 hydroxylase deficiency and 17-hydroxylase deficiency), hypothyroidism, hyperthyroidism, hyperparathyroidism, acromegaly, carcinoid syndrome, porphyria, psychogenic hyperventilation, burns, acute pancreatitis, alcohol withdrawal, sickle cell crisis, post-cardiopulmonary resuscitation, postoperative hypertension, polycythemia, the syndrome of inappropriate antidiuretic hormone secretion and posttransfusion. None of these are consistent with the patient's presentation.

Hypoglycemia as the cause of hypertension is a possibility given the patient's change in mental state and recent change in diabetic therapy. If this were the case, however, one would expect a low admission serum glucose level and a response in mental state to an infusion of 50% glucose solution. In addition, unless the patient's hypoglycemia remained uncorrected, one would not expect the hypertension to be paroxysmal and protracted while the patient was in hospital.

A variety of drugs, foods and poisons may cause hypertension. Included in this list are licorice (glycyrrhizic acid), phenylpropanolamine hydrochloride, phencyclidine hydrochloride, food high in tyramine when taken with monoamine oxidase inhibitors, ethylene glycol and lithium. There is no history that he ingested these substances, however, and a toxicology screen was negative.

Figure 2.—A computed tomographic scan of the abdomen with contrast. The arrow points to the left adrenal mass.

Conclusion

This patient's presentation is most suggestive of a pheochromocytoma. Other disease processes discussed are possible—renovascular hypertension, primary aldosteronism, Cushing's syndrome, hypoglycemia and ingestion of a sympathomimetic drug—but not likely. The possibility of brain tumor causing this syndrome is intriguing from a pathophysiologic standpoint but, as mentioned, the absence of premonitory symptoms, papilledema or localizing signs and the transitory nature of the patient's mental state changes are against this diagnosis.

Diagnostically, I would do a spot urine analysis for metanephrines because this is the best screening procedure for pheochromocytoma and this catecholamine metabolite is least affected by interfering substances.[33] Results from a single voided urine specimen correlated closely with those found on a 24-hour urine specimen. The finding of normal urine catecholamine levels during a paroxysm of hypertension excludes pheochromocytoma. Plasma catecholamines can be measured by a radioenzymatic technique or liquid chromatography with electrochemical detection but are reported to have 20% false-negative values.[34] Administering clonidine hydrochlo-

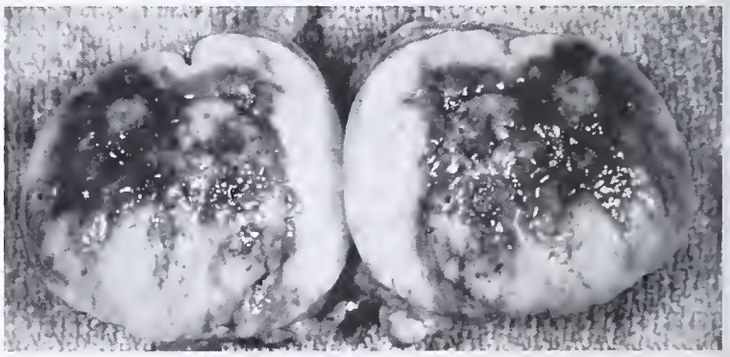

Figure 3.—The gross surgical pathologic specimen shows intraparenchymal hemorrhage.

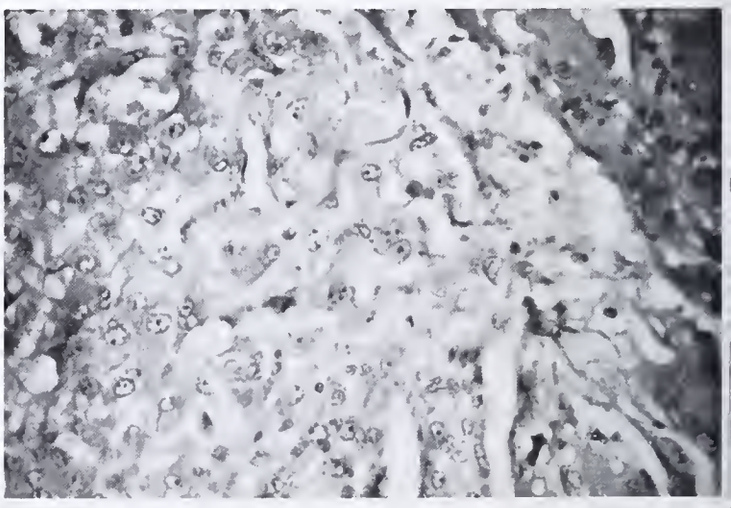

Figure 4.—Microscopic examination of the left adrenal mass shows a chromaffin cell tumor (hematoxylin-eosin stain, magnification × 125).

ride will suppress plasma catecholamines in those patients without a pheochromocytoma but will not suppress catecholamines in those patients with a tumor.[35] Finally, pheochromocytoma can usually be adequately localized by CT scan, and other procedures such as intravenous pyelogram or aortography are rarely needed.

Clinical Course

DR ENG: Urinary metanephrine and vanillylmandelic acid levels were 18,614 μg per 24 hours (normal 0 to 1,000) and 41.8 mg per 24 hours (normal 2 to 10), respectively. The plasma norepinephrine level was 21,760 pg per ml (normal 110 to 410) and the plasma epinephrine level was 12,200 pg per ml (normal <50). Plasma levels of dopamine were not elevated. A CT scan of the abdomen showed a 4-cm left adrenal mass (Figure 2). Before the surgical procedure the patient's blood pressure was controlled with the administration of phenoxybenzamine hydrochloride and propranolol. At the operation a mass was found superior to the left kidney (Figure 3) that on pathologic examination showed a chromaffin cell tumor consistent with pheochromocytoma (Figure 4). Mild diastolic hypertension was noted postoperatively, but results of a 24-hour urine collection for metanephrines and vanillylmandelic acid were within normal limits. Echocardiograms done five months after the operation showed normalization of left ventricular dimensions with a septal thickness of 1.0 cm and a posterior wall thickness of 1.0 cm.

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Medical Staff Conference

Bronchoalveolar Lavage

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

FLOYD C. RECTOR:* *The topic of this Medical Staff Conference is "Bronchoalveolar Lavage," and the discussant will be Dr Jeffrey Golden, Adjunct Professor of Medicine in Pulmonary Medicine.*

JEFFREY GOLDEN, MD:† The purpose of this discussion is to answer the question, "What can we learn about pulmonary disease by washing or lavaging the periphery of the lung and analyzing the derived cellular and noncellular constituents of the fluid recovered?" First, I will review the technique of lavage; second, I will discuss the utility of lavage as a diagnostic procedure, and, finally, I will review the use of lavage to increase our understanding of interstitial lung diseases. In this final section, I will emphasize its role in assessing the presence and extent of alveolar wall inflammation, or alveolitis, discussing what we might learn from serial lavages about the natural history and the success of therapeutic manipulations for parenchymal infiltrative lung diseases, such as sarcoidosis.

In terms of technique, bronchoalveolar lavage (BAL) is one of several specific manipulations made possible by the flexible fiber-optic brush biopsy, transbronchial biopsy and, most recently, transtracheal aspiration biopsy. Transbronchial biopsy is useful for obtaining a specimen of lung parenchyma and involves passing biopsy forceps through the bronchoscope and actually taking a biopsy specimen through a small peripheral airway to obtain lung tissue. The transtracheal aspiration biopsy, developed by Wang and co-workers, enables biopsies to be done of mediastinal and hilar lymph nodes and masses directly through large proximal airways.[1] The problem with such invasive bronchoscopic procedures is the potential for complications such as bleeding and pneumothorax. This potential for complications has, in part, stimulated enthusiasm for BAL, a relatively benign invasive procedure. A BAL is done simply by wedging the tip of the bronchoscope into a segmental or subsegmental airway and instilling and aspirating normal saline solution. The constituents of the fluid recovered are illuminating in both clinical and research assessments of the infiltrative or "interstitial" parenchymal lung disease.

Lavage as a Diagnostic Procedure

As a diagnostic procedure, lavage is useful primarily for identifying the cause of infection. There are a few parenchymal lung diseases, not classically of infectious origin, where lavage can obtain diagnostic material, obviating the need for lung tissue—alveolar proteinosis and eosinophilic granuloma. A BAL done recently in a patient with a two-year history of progressive shortness of breath and parenchymal infiltrates on chest roentgenogram contained material that stained for periodic acid-Schiff, which is pathognomonic for alveolar proteinosis.[2] Following therapeutic lavage of each of her lungs with 30 liters of saline solution under general anesthesia, she had dramatic relief of dyspnea and an increase in her vital lung capacity from 600 ml to 1,700 ml. Another young woman presented with a history of multiple pneumothoraces and an upper lobe infiltrate on chest roentgenogram. Ultrastructural evaluation of her BAL revealed the so-called histiocytosis X cells as shown by their cleft nuclei and "X bodies" throughout the cell cytoplasm.[3] In this case, BAL led to a diagnosis of eosinophilic granuloma.

Usually BAL is used as a diagnostic tool in evaluating for possible pulmonary infections. This use is illustrated by our approach to a renal transplant patient on an immunosuppressive regimen in whom shortness of breath developed and who had diffuse nodular infiltrates on a chest roentgenogram (Figure 1). Although the patient had severe hypoxemia, we were able to do bronchoalveolar lavage and found the fluid to contain both *Pneumocystis carinii* and coccidioidomycosis organisms. The need to obtain lung tissue by either transbronchial biopsy or an open-lung biopsy was obviated by the BAL results. Recently Stover and colleagues reviewed the usefulness of BAL in a series of such patients.[4] In 92 immunocompromised patients presenting with diffuse pulmonary infiltrates on chest roentgenogram, bronchoscopy utilizing transbronchial biopsy, brush biopsy and lavage gave a specific infectious diagnosis 83% of the time. In evaluating the diagnostic yield of BAL in comparison to the more dangerous transbronchial biopsy, BAL alone had a 66% yield for spe-

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
BAL = bronchoalveolar lavage

eific diagnoses. Transbronchial biopsy, which could not be done on a third of these patients because of hypoxia, thrombocytopenia or both, had a similar yield of 60% specific diagnoses. Ideally both bronchoscopic procedures should be done. When biopsy is contraindicated, such as because of mechanical ventilation with positive airway pressure, thrombocytopenia or profound hypoxemia, BAL alone, without transbronchial biopsy, may be diagnostic.

Our data at the University of California, San Francisco, also support the usefulness of BAL as an effective diagnostic tool.[5-8] To compare BAL with transbronchial biopsy, we evaluated 171 patients with the acquired immunodeficiency syndrome (AIDS) with respiratory symptoms in whom opportunistic pulmonary infection was suspected. Bronchoscopy including both BAL and transbronchial biopsy detected 96% of the pathogens causing pneumonia among these patients. BAL and transbronchial biopsy had similar individual yields of 85% and 87%, respectively. For transbronchial biopsy there were 17 false-negatives; for BAL there were 9 false-negatives—about half as many as with transbronchial biopsy. For example, among our first 18 patients with *P carinii* pneumonia complicating AIDS, all patients were diagnosed by lavage; four had a false-negative report of a transbronchial biopsy in the presence of abnormalities noted with BAL.

In view of the usefulness of BAL, I am not sure whether transbronchial biopsy is needed in addition to BAL in patients with AIDS. Perhaps because their infections are so fulminant, patients with AIDS are unfortunately very easy to diagnose with BAL alone. For this reason Gamsu, Wong and I are now working on a catheter system to enable lavage at the bedside without the need of a fiber-optic bronchoscope and the complexity of fluoroscopic guidance. In a small preliminary project, Caughey joined us to study the yield of catheter lavage in nine patients with AIDS. In each patient, we compared the results of nonbronchoscopic catheter lavage in one lung with those of full fiber-optic bronchoscopy in the other lung using transbronchial biopsy, lavage and bronchial brushing.[9,10] The BAL specimen obtained with the catheter alone was as productive as any of the specimens obtained by bronchoscopy. Because the catheter technique is cheaper and safer than a complete fiber-optic bronchoscopy, we hope that it will soon be ready to help deal with the pulmonary infections associated with the growing number of patients with AIDS.

The following cases further exemplify the utility of BAL as a diagnostic modality. A young surgeon from Central America with metastatic adenocarcinoma presented with a chest roentgenogram showing diffuse nodular infiltrates. He underwent bronchoscopy, and although the results of the transbronchial biopsy were normal, the BAL showed *Strongyloides*. The planned chemotherapy might well have caused dissemination of this filarial infection.

Another recent and unusual example of the diagnostic usefulness of BAL involved a 33-year-old scuba diving instructor who presented with mild hemoptysis. Because her chest roentgenogram showed nodular lesions primarily in the right upper lobe (Figure 2), she underwent bronchoscopy. We thought this chronic right upper lobe process was most likely due to a granulomatous disorder, such as eosinophilic granuloma, tuberculosis, sarcoidosis or the like. A transbronchial biopsy specimen showed no abnormalities but a BAL specimen showed mucoid *Pseudomonas aeruginosa*. This unusual infection and the additional history of sinusitis led us to do a pilocarpine iontophoresis. The striking elevation in sweat chloride concentration established a diagnosis of cystic fi-

Figure 1.—A chest roentgenogram of a renal transplant patient shows diffuse nodular densities. The patient was found to have both *Pneumocystis carinii* pneumonia and coccidioidomycosis by bronchoalveolar lavage.

Figure 2.—A chest roentgenogram of a 33-year-old athletic woman shows upper lobe nodular infiltrates. The patient underwent bronchoalveolar lavage, results of which showed *Pseudomonas aeruginosa* and led to a laboratory diagnosis of cystic fibrosis (see text).

brosis. I expect there are few 33-year-old scuba divers with cystic fibrosis.

The hazards of BAL are minimal. Strumpf and associates reviewed 281 BAL procedures and found a complication rate of less than 5%, most complications being trivial; one patient may have had a postlavage pneumonitis.[11] Further, Rankin and co-workers showed that BAL is safe even among patients with asthma with hyperreactive airways.[12] He and his colleagues instilled 300 ml of saline solution in each lung and found no bronchospasm or change in pulmonary physiology among these patients. Clearly, BAL is becoming recognized as an effective and safe diagnostic procedure.

Bronchoalveolar Lavage and Interstitial Lung Disease

A rapidly growing application for BAL is in defining the cellular physiology associated with parenchymal or "interstitial" lung diseases. With the exception of sarcoidosis, most chronic diffuse parenchymal lung disease cannot be diagnosed by bronchoscopy with transbronchial biopsy. Once a specific diagnosis is made, however, BAL offers a mechanism for assessing such diseases serially over time, providing information on the natural history of these processes and on the benefit of therapeutic manipulation.

It should be made clear that the term "interstitial lung disease" is a misnomer. The alveoli are lined by epithelial cells resting on a basement membrane separated by an interstitial space from the basement membrane of the endothelial cells of an alveolar capillary. This interstitial space between an alveolar capillary and the epithelium is certainly involved in diffuse parenchymal lung disease, but there is no disease that afflicts only the interstitium of the lung. Instead, the various "interstitial" lung diseases involve the alveolar capillaries, the epithelium lining the air spaces, the alveolar air spaces and the small airways just proximal to the alveoli. It is the involvement of the alveolar air spaces by these peripheral lung diseases that permits them to be sampled with BAL.

Parenchymal lung disease appears to begin with inflammation in the periphery of the lung that in time progresses to fibrosis and, finally, to end-stage "honeycomb" lung. Studies of humans and animals using BAL have shown that the lung can function as an independent immune organ.[13-15] In the case of sarcoidosis, the lung generates chemotactic factors that recruit from the peripheral blood various inflammatory cells into the lung parenchyma, culminating in alveolitis. The injury that initiates this sequence is unknown for sarcoidosis and for idiopathic pulmonary fibrosis. In asbestosis, the injury is probably initiated by intracellular ingestion of inhaled asbestos fibers. But whatever the inciting event, the resultant alveolitis is thought to be the initial step leading ultimately to diffuse pulmonary fibrosis. With the development of fibrosis and honeycombing, interstitial diseases become difficult if not impossible to treat. The hope is that earlier detection of disease, when alveolitis has first begun, may lead to better results of therapy. By providing a specimen with a cellular composition of the process affecting the lung periphery, BAL permits assessment of the presence of possibly reversible alveolitis, and serial studies may provide clues as to the effectiveness of anti-inflammatory agents.

To begin a discussion of BAL findings in sarcoidosis and interstitial pulmonary fibrosis, I will review the results of BAL in normal volunteers.[16] In a normal subject, the instillation and aspiration of 100 ml of saline solution samples about a million alveoli. On average, about 50% of the fluid instilled is recovered. The cell differential in a lavage specimen normally contains 93% macrophages, less than 10% lymphocytes and few polymorphonuclear leukocytes (unless the patient is a cigarette smoker). With this background, I will now discuss two basic types of alveolitis. The first will be the lymphocytic alveolitis associated with sarcoidosis, and the other is the neutrophilic alveolitis associated with idiopathic pulmonary fibrosis.

BAL and Sarcoidosis—Lymphocytic Alveolitis

Bronchoalveolar lavage has provided much new information on the cellular physiology and natural history of sarcoidosis. This information may help determine whether the use of steroids produces long-term benefit in patients with progressive pulmonary involvement, a question that is still unresolved. In a study by Thrasher and Briggs of sarcoid patients followed over a five-year period, 8% of the patients died of lung disease, 22% had progressive infiltration on chest roentgenograms and 70% had resolution of chest roentgenographic abnormalities.[17] At least 30% of the patients in this series had significant sequelae from what is erroneously referred to as a benign disease. On presentation, it is currently impossible to predict which sarcoid patients will have resolution and which will have progression to end-stage honeycomb lung. Some evidence suggests, however, that BAL may offer a way to predict future deterioration.

Sarcoidosis begins as a lymphocytic granulomatous alveolitis that resolves with a variable degree of fibrosis.[18] Bronchoalveolar lavage early in the course of the disease, at the time of active alveolitis, shows an increased percentage of lymphocytes.[13] The cellular composition of a BAL specimen is very similar to that from an extract of an open-lung biopsy,[19] suggesting that BAL fluid closely approximates an open-lung biopsy specimen. This is fortunate, for serial BAL over time is practical, whereas serial open-lung biopsy is not. Serial BAL also seems preferable to serial pulmonary function studies, including advanced studies such as gas exchange with exercise. These tests enable assessment of the presence and degree of lung impairment, but they provide no information enabling a distinction between fibrosis and cellularity as a cause of dysfunction.[20]

Although BAL has not yet been shown to alter importantly the clinical management of sarcoidosis, it has helped to define the nature of the alveolitis associated with the disease. The lymphocytosis characterizing the alveolitis of sarcoidosis primarily involves T lymphocytes.[13,19] Subset enumeration of these T lymphocytes shows an increased helper to suppressor T-cell ratio.[21] Further, the helper T cells obtained by BAL are activated and spontaneously secrete lymphokines such as monocyte chemotactic factor.[13] Further evidence of the activation of BAL-derived lymphocytes in sarcoidosis is the presence of Fc receptors for immunoglobulin G[13] and of surface markers that enhance rosette formation with sheep erythrocytes.

Studies of BAL specimens from patients with sarcoidosis confirm that the lung can function as an independent immune organ. In contrast to the increased pulmonary accumulation

of activated lymphocytes with an increased helper to suppressor T-cell ratio, a peripheral blood specimen shows lymphopenia with a *decreased* helper to suppressor T-cell ratio.[13] As further evidence that the lung in patients with sarcoidosis operates as an independent immune organ, BAL-derived lymphocytes secrete 24 times more monocyte chemotactic factor than do peripheral blood lymphocytes from the same patient.[19] Finally, BAL-derived lymphocytes but not peripheral blood lymphocytes have been shown to release spontaneously interleukin 2, a product that causes a clonal increase of the T-lymphocyte pool.[22]

Although lymphocytosis is seen in the BAL specimen from patients with sarcoidosis, the most commonly found cell in a BAL specimen, as in that from normal volunteers, is the macrophage. In sarcoidosis, however, lung macrophages are spontaneously activated. In patients with "high-intensity alveolitis"—arbitrarily defined as a BAL lymphocyte differential of more than 28%—recovered alveolar macrophages spontaneously release interleukin 1.[23] Interleukin 1, or T-lymphocyte growth factor, modulates local T-cell accumulation,[21] thus further contributing to the development of a lymphocytic alveolitis.

In addition, BAL affords information as to how macrophages and lymphocytes interact. Macrophages and lymphocytes will interact only if they have homology at their respective genetic loci of immune response genes, which are located near the histocompatibility locus D. Encoded from that genetic locus onto the surface of macrophages is a so-called D antigen, also known as Ia (immune-associated antigen). Lymphocytes will only interact with macrophages that have this D surface antigen on their cell surface displaying homology of their immune response genetic loci.[24]

In summary, analysis of BAL specimens from patients with sarcoidosis has shown that the lung acts as an independent immune organ. An unknown agent stimulates the development of an alveolitis composed of active lymphocytes that spontaneously secrete monocytic chemotactic factor. Monocytes and alveolar macrophages in turn secrete interleukin 1, which further promotes the lymphocytic alveolitis. Finally, lavage has been revealing as to how lymphocytes and macrophages interact by way of homology of their immune response genes. Clearly, BAL has been helpful in providing an understanding of the cell-to-cell "sociology" affecting the lungs in sarcoidosis.

Sarcoidosis—Clinical Relevance of Bronchoalveolar Lavage

New clinical information provided by BAL findings in patients with sarcoidosis may lead to a better understanding of the natural history of this disease and to a means of monitoring the response to therapeutic manipulations. In a recent clinical study, Keogh and associates showed that patients with an intense lymphocytic alveolitis, as defined by BAL findings, have a more rapid physiologic deterioration over a six-month period than those with less intense alveolitis.[25] Of note, these two groups of sarcoidosis patients, those with high- and low-intensity alveolitis, were indistinguishable at the start of this study by conventional clinical means, including roentgenographic and physiologic analysis. Further, Baughman and colleagues showed that sarcoidosis patients with increased helper T cells in BAL fluid had a greater improvement in vital capacity with corticosteroid therapy.[26] As in the study by Keogh and co-workers, results of the initial clinical, roentgenographic and pulmonary function evaluation could not predict a subsequent response to corticosteroids. Unlike the direct assessment of the alveolitis provided by BAL, these classic methods cannot distinguish between active inflammation and irreversible fibrosis.

Similarly, Ceuppens and colleagues showed that the increased helper to suppressor T-cell ratios found in BAL fluid from sarcoid patients decreased with prednisone therapy.[21] Prednisone is known to suppress helper T cells.[27] Of note, although untreated sarcoidosis patients had an increased number of helper T cells in their lungs, their peripheral blood actually had fewer helper T cells, suggesting that in sarcoidosis there is active pooling of helper T cells in the lung and depletion of such cells in the peripheral blood. This is consistent with the concept that the lungs operate as an independent immune organ in sarcoidosis. Further, in the study by Ceuppens and co-workers, untreated sarcoidosis patients with spontaneous clearing of their chest roentgenogram also had a decrease in the number of helper T cells as assessed by BAL.[21] Further, in patients with spontaneous resolution of sarcoidosis, the decrease in the number of BAL helper T cells preceded radiographic and clinical improvement.

Although the above studies are all preliminary, they nevertheless suggest that BAL may predict the subsequent clinical course of individual patients with sarcoidosis.

BAL and Idiopathic Pulmonary Fibrosis—Neutrophilic Alveolitis

In contrast to sarcoidosis, which is associated with a lymphocytic alveolitis, a neutrophilic alveolitis is associated with other infiltrative lung diseases, such as idiopathic pulmonary fibrosis, asbestosis and lung disease associated with collagen vascular diseases. This is mirrored in BAL fluid as an increase in the differential percentage of neutrophils.[28,29] Idiopathic pulmonary fibrosis provides an example of such processes. Lung pathology associated with idiopathic pulmonary fibrosis involves variable degrees of cellular infiltration and fibrosis. The nomenclature is confusing. If pathology studies reveal only cellular infiltration, the process is referred to as desquamative interstitial pneumonitis. If they show only fibrosis, the process is called usual interstitial pneumonitis. Most cases of idiopathic pulmonary fibrosis are a varying combination of cellular infiltration and fibrosis. To complicate further the nomenclature, the British refer to idiopathic pulmonary fibrosis as "cryptogenic fibrosing alveolitis," which by definition includes both usual interstitial pneumonitis and parenchymal lung diseases associated with collagen vascular processes, such as lupus erythematosus.[29]

As in the case of sarcoidosis, BAL has been of benefit in understanding the cellular physiology involved in idiopathic pulmonary fibrosis. Alveolar macrophages secrete neutrophil chemotactic factor, which recruits peripheral polymorphonuclear leukocytes to the lung where these cells release enzymes such as collagenase and neutral proteases that result in lung damage.[30,31] For example, BAL-derived macrophages from patients with high-intensity leukocytic alveolitis, defined as at least 10% neutrophils in a BAL differential cell count, spontaneously secrete neutrophil chemotactic factor.[30] Further, several experiments involving BAL suggest that immune

complexes activate alveolar macrophages to secrete neutrophil chemotactic factor. First, BAL fluid specimens from patients with idiopathic pulmonary fibrosis contain immune complexes. Second, these immune complexes induce normal alveolar macrophages to secrete neutrophilic chemotactic factor. Third, there is a significant correlation between the release of neutrophil chemotactic factor by BAL-derived alveolar macrophages and the amount of immune complexes contained in BAL specimens. Finally, the finding that the alveolar macrophages that release neutrophil chemotactic factor have suppression of their immunoglobulin G Fc-receptor function suggests that immune complexes are bound to the surface of these alveolar macrophages.[30]

In addition to elucidating possible pathophysiologic features, BAL may have clinical relevance in the approach to patients with idiopathic pulmonary fibrosis. Keogh and colleagues followed such patients on prednisone therapy for one year. After the year of therapy, the condition of those patients with a persistent neutrophilic alveolitis had deteriorated clinically and physiologically, in contrast to that of patients with less active alveolitis.[32] Intermittent high-dose prednisone therapy resulted in a decrease in their neutrophilic alveolitis over a six-month period.[33] The relevance of the diminution of the neutrophilic alveolitis with this therapy is not clear, however, as clinical, roentgenographic and physiologic assessments did not show that these patients' condition had improved over this six-month period.

Clinical studies from Britain have thrown into question the clinical relevance of finding a high percent of neutrophils in BAL fluid from patients with idiopathic pulmonary fibrosis.[34] In these studies, therapeutic effectiveness in these patients was better predicted by the *lymphocytic* rather than *neutrophilic* content of BAL fluid. In this study, 75% of patients with idiopathic pulmonary fibrosis with lymphocytic alveolitis responded to steroid therapy, whereas patients who had neutrophilic alveolitis or the absence of an increased number of lymphocytes in their BAL cell differential tended not to respond to steroid therapy.

The disparity in findings in studies from the National Institutes of Health and in those from Britain may be due to differences in method. Differential cell counts in BAL fluid differ between laboratories, depending on the techniques of BAL processing. For example, the number of lymphocytes counted in BAL fluid is affected by the speed of the centrifugation of the specimen.[35] Further, using cell mixtures of known composition, more accurate differentials of BAL-derived cell populations were obtained with millipore filter preparations than with cytocentrifuge preparations.[36] Cytocentrifugation appears to result in a selective loss of lymphocytes. To complicate further the interpretation of BAL results, there is heterogeneity of bronchoalveolar lavage cellularity in parenchymal lung diseases, such as sarcoidosis, depending on which segment of the lung is assessed.[37] Further, bronchoalveolar lavage cellularity may change with the state of parenchymal lung disease. For example, patients with advanced pulmonary sarcoidosis may have a neutrophilic alveolitis rather than the lymphocytic alveolitis noted in patients with less advanced disease.[38] Clearly, if BAL can be considered a clinically useful tool both in assessing the natural history of disease and in determining the benefit of therapy, methodologic problems must be eliminated.

Bronchoalveolar Lavage—Utility as a Research Tool

Although preliminary, research utilizing BAL has already been enlightening in terms of the general problem of assessing the presence and the mechanism of lung injury. As discussed previously, BAL may help with the management of patients with "interstitial" lung diseases such as sarcoidosis and idiopathic pulmonary fibrosis. Different patterns of BAL cell differential in other interstitial lung diseases are emerging. Analysis of a BAL specimen from a patient with eosinophilic pneumonia shows an increased percentage of eosinophils. This may obviate the need for more invasive diagnostic procedures in a patient who presents with cough and a chest roentgenogram showing the classic "reverse pulmonary edema pattern" usually evident with this process. Furthermore, serial lavage may allow monitoring of this eosinophilic alveolitis and predict an imminent recurrence of this process before the development of shortness of breath. As eosinophilic pneumonia tends to recur, the early application of steroid therapy with BAL evidence of recurrent eosinophilic alveolitis may minimize lung injury consequent to a delay in therapy until clinical and roentgenographic manifestation of this disease becomes more evident.[39]

Similarly, other clinical problems such as pulmonary drug toxicity may be defined and serially evaluated by BAL. The development of amiodarone lung toxicity may be monitored by BAL.[40] Preliminary experience in animals also suggests the potential future clinical usefulness of BAL assessment of angiotensin-converting enzyme as an index of pulmonary toxicity in patients receiving bleomycin.[41]

In the field of occupational and environmental medicine, BAL is emerging as a useful tool to investigate lung injury. BAL fluid obtained from patients with asbestosis and from animals exposed to asbestos fibers suggests the presence of a neutrophilic alveolitis.[42,43] Also, a BAL study has shown that macrophages that have ingested asbestos fibers release neutrophil chemotactic factor, possibly facilitating the development of a neutrophilic alveolitis.[44] Further, BAL specimens from animals exposed to asbestos fibers reveal that the ingestion of asbestos fiber stimulates macrophages to release phospholipase A and prostaglandin E_2, both possible mediators of lung inflammation.[45] Finally, other experiments in animals involving BAL unequivocally show that there is progressive lung injury due to asbestos long after asbestos exposure has ceased.[46] Clinically, quantitative analysis of asbestos bodies in BAL fluid may correlate with the development of specific sequelae of prior asbestos exposure; the presence of asbestos bodies on a BAL specimen can clearly disclose unknown asbestos exposure better than can the use of history and questionnaire.[47]

BAL is also useful in evaluating other environmental parenchymal lung diseases such as hypersensitivity pneumonitis. In established cases of hypersensitivity pneumonitis, a BAL specimen shows an increased percentage of lymphocytes. Further, BAL fluid from patients with pigeon-breeder's disease shows that BAL-derived lung lymphocytes better reflect the immunologic response to pigeon antigen than do peripheral blood lymphocytes.[48] This is again consistent with the concept of pulmonary rather than systemic cell-mediated hypersensitivity to antigens and again shows that the lung can function as an independent immune organ.

Assessing a BAL specimen in asymptomatic farmers with positive precipitins to *Micropolyspora faeni,* the antigen of farmer's lung disease, can potentially detect the presence of early alveolitis and perhaps can someday be used as a screening test to identify persons at great risk from direct exposure to the culpable antigen.[49] Further, the lymphocytes composing the alveolitis of hypersensitivity pneumonitis are primarily T cells. Helper and suppressor T-cell subset enumeration shows an increase in suppressor T cells, differentiating the alveolitis of hypersensitivity pneumonitis from that of sarcoidosis, a disease that can easily be confused on a pathologic basis with hypersensitivity pneumonitis.[50] Similarly, berylliosis is another example of an immune-mediated environmental parenchymal lung disease that can easily be confused with sarcoidosis. The lymphocytes contained in a BAL specimen from patients with berylliosis proliferate in response to exposure to beryllium compounds more than do peripheral blood lymphocytes. Such functional analysis of BAL-derived lymphocytes may be more helpful in diagnosing disease like berylliosis than is the tissue obtained at the time of open biopsy.[51]

Finally, BAL has proved useful in examining other types of environmental lung disease. For example, I and my colleagues have shown that in normal human volunteers a transient increase in bronchial reactivity will develop on exposure to ozone, a major air pollutant in urban areas.[52] BAL fluid obtained from such subjects discloses a striking increase in neutrophils.[53] This suggests that airway inflammation with polymorphonuclear leukocytes may have fundamental importance in the development of occupational asthma.

Conclusion

The ultimate utility of bronchoalveolar lavage remains unknown. Clearly, it has already been shown to have an important role in evaluating pulmonary infections. As a useful tool in expanding our understanding of parenchymal lung disease, BAL is becoming more and more appreciated. Currently, however, its clinical usefulness in the management of parenchymal or interstitial lung disease will not be established[54,55] until the methodologic problems regarding the analysis of BAL fluid are resolved.

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Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Neurostimulation for Treatment of Urethral Sphincter Spasticity

QUESTION:

Is electrical stimulation of the sacral nerve root accepted medical practice for treatment of urethral sphincter spasticity?

OPINION:

In the opinion of the Scientific Advisory Panel on Urology, the concept and methodology of electrical stimulation of the sacral root for the treatment of urethral sphincter spasticity is established and can be considered accepted medical practice when done on carefully selected patients by physicians who are trained in the technique. Candidates for this treatment include a variety of patients with neurogenic urinary dysfunction whose disorder continues to be disabling and unresponsive to other, more conventional methods.

There have been numerous attempts at manipulation of the various elements of pelvic floor spasticity, external sphincter spasticity and voiding dysfunction by neural stimulation. The procedure has been done at various medical centers with varying rates of success and low complication rates. Neurostimulation of the sacral root is unique in that it is a natural rather than a mechanical approach to control the muscles involved in urination.

The principle upon which neurostimulation is based is not new. Release of pain and spasticity by electrical stimulation is a well-accepted surgical technique. The application of this principle to relieve pain and spasticity in the urinary tract, therefore, is similar to its application in other parts of the body. As developed by the University of California, San Francisco, after many years of research, the electronic bladder pacemaker is surgically implanted and provides electrical stimulation to key nerves in the sacral root responsible for urination. The patient activates the pacemaker by remote control "on demand" via a hand-held external unit. It is designed to restore three functions to the impaired bladder: reservoir capability, sphincter muscle control and complete evacuation of urine. Although the number of patients treated by this method has been small, study results have shown the pacemaker to be successful in meeting the first two objectives. The ability to evacuate all urine has not been as successful and is the focus of ongoing investigation.

Epitomes
Important Advances in Clinical Medicine

Pathology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in pathology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in pathology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pathology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Immunohistochemistry and the Diagnosis of Spindle Cell Neoplasms

THE HISTOLOGIC DIAGNOSIS of poorly differentiated or unusual neoplasms by traditional methods may be difficult, relying on routine paraffin-embedded, hematoxylin-eosin-stained tissue sections augmented by special stains or ultrastructural examination or both. Recent advances in immunohistochemistry have added another dimension to tumor evaluation, giving immunologic clues to the diagnosis and decreasing the volume of cases previously examined by electron microscopy.

The antibodies generally used in immunohistochemistry are myriad, directed against structural "intermediate filaments" (keratin, vimentin, desmin, neurofilaments and glial fibrillary acidic protein), enzymes (such as neuron-specific enolase), other proteins (such as factor VIII, S-100) and other material. The literature, replete with immunologic characterization of various tumors, shows that few, if any, antibodies that have been developed are actually "specific" to a particular tumor. Despite this, immunohistochemistry is a powerful tool, especially when used to answer specific questions or to narrow a differential diagnosis formulated by review of more traditionally prepared material.

For example, the differential diagnosis of a spindle cell neoplasm arising in deep soft tissues and growing in long, sweeping fascicles includes fibrosarcoma, synovial sarcoma, leiomyosarcoma and malignant schwannoma. A battery of immunoperoxidase stains would show vimentin positivity in each because all are felt to be of mesenchymal origin. Of the four, only synovial sarcoma expresses cytokeratins—a finding similar to only three other mesenchymal tumors: mesothelioma, epithelioid sarcoma and adenomatoid tumor. The smooth muscle-derived leiomyosarcoma generally expresses desmin, whereas malignant schwannoma, being of neural crest derivation, reacts for S-100 protein. If all of the stains were negative (except for vimentin) then fibrosarcoma would be seriously considered.

The differential diagnosis of spindle cell tumors that occur more superficially in the subcutis or cutis includes melanoma, squamous carcinoma and several mesenchymally derived neoplasms including dermatofibroma, dermatofibrosarcoma protuberans, leiomyoma and leiomyosarcoma. Melanoma may be distinguished by its expression of S-100 protein and vimentin, while epithelial-derived squamous carcinoma produces only cytokeratin. The smooth muscle tumors show desmin and vimentin positivity whereas histiocytic markers such as α_1-antitrypsin, lysozyme and α_1-antichymotrypsin are generally found in dermatofibroma and dermatofibrosarcoma protuberans.

As techniques improve and antibodies are developed that are more tumor-specific, immunohistochemistry will become an even more powerful tool, improving the reproducibility of diagnosis in these and other difficult tumors.

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Barrett's Esophagus

BARRETT'S ESOPHAGUS is the eponym for replacement of the squamous epithelium of the distal esophagus by columnar epithelium. This replacement is now considered to be an acquired metaplasia that follows the epithelial injury caused by chronic gastroesophageal reflux and can therefore often be associated with strictures or peptic ulceration of the esoph-

agus. The exact prevalence is not known, but Barrett's esophagus is found in about 10% of patients undergoing esophagoscopy for symptoms of reflux.

On histologic examination, Barrett's esophagus has a heterogeneous appearance and comprises a variety of cell types similar to gastric and intestinal epithelial cells. A distinctive histologic pattern of goblet cells interspersed among columnar mucous cells is common and virtually diagnostic of Barrett's esophagus. Other patterns resemble gastric fundic or cardiac mucosa and can thus be interpreted as Barrett's esophagus only when the site of biopsy is definitely the esophagus and not a hiatus hernia.

This condition is clinically important because of its association with esophageal adenocarcinoma. In recent studies, a 30 to 40 times increased risk was estimated when Barrett's esophagus is present. Because these figures are based on a relatively short follow-up period, the actual risk may be even higher. Such considerations have led to the suggestion that biopsies be done regularly on patients with Barrett's esophagus to look for epithelial dysplasia, which, as a putative precursor of adenocarcinoma, would serve to identify those patients at highest risk for malignancy. Problems with this suggestion include the lack of well-defined histologic criteria for recognizing dysplasia and distinguishing it from reactive or regenerative changes. Nevertheless, high-grade dysplasia has recently been shown to represent a morphologic marker of risk for esophageal adenocarcinoma.

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The Carcinoma-Carcinoid Spectrum

IN THE PAST DECADE we physicians have become aware that carcinoid tumors show a much wider clinicopathologic spectrum than previously thought. This has given rise to a plethora of new terms, some of which, such as apudoma, neurochristoma and neuroendocrinoma, are based on their postulated neuroectodermal derivation; others, such as neuroendocrine carcinoma, on their clinical behavior, and a group, such as gastrinoma, on their secretion products. Because these tumors are morphologically distinctive, I see no point in changing Obendorfer's original terminology, and thus I designate these lesions as carcinoids and specify their differentiation and secretion products (Table 1).

On histologic examination, some tumors may show atypical features such as glandular profiles, a spindle cell pattern, squamous or osteoid metaplasia or pleomorphism with frequent mitoses and necrosis. In rare cases they may be poorly differentiated and resemble undifferentiated large-cell or small-cell carcinoma (oat cell carcinoma) and lymphoma. As is well known, some carcinoids are associated with well-defined syndromes, such as the carcinoid or the Zollinger-Ellison syndromes, due to the secretion of amines or peptides. Immunohistochemical analysis of these tumors has shown that, whereas one amine or peptide may predominate, such as serotonin or gastrin, most are multihormonal. These findings

TABLE 1.—*Nomenclature and Classification of Pure and Mixed Endocrine Cell Tumors*

- Carcinoid tumors
  - Well differentiated
  - Moderately differentiated
  - Poorly differentiated
    - Small cell (oat cell)
    - Large cell
- Mixed (composite) glandular-endocrine cell carcinoma
  - Microglandular-goblet cell carcinoma
  - Scirrhous-argyrophil cell carcinoma
  - Adenoendocrine cell carcinoma
- Amphicrine cell carcinoma

are also seen with the clinically silent carcinoids such as the foregut and hindgut tumors. Furthermore, the immunohistochemically shown amines and peptides in the primary tumor do not necessarily correspond to those found in the overlying endocrine cells or in metastatic lesions.

Although the presence of scattered endocrine cells within adenomas and carcinomas of the gastrointestinal tract has been known for some time (in as many as 20% of all colonic carcinomas), there are a number of tumors in which there is a large admixture of endocrine and epithelial cells. Thus, the strict separation of gut mucosal tumors into carcinoma and endocrine tumors has had to be modified to include those tumors with admixtures of varying proportions of endocrine and epithelial cells. These tumors have been designated as mixed or composite tumors and have been further subdivided into several distinctive histologic types (see Table 1). Some of these tumors, such as the microglandular-goblet cell carcinoma, have a distinctive clinical behavior, whereas others, such as the scirrhous-argyrophil and adenoendocrine cell carcinoma, appear to behave in a manner similar to the corresponding carcinoma. Finally, there is a further distinctive tumor type, namely the amphicrine tumors. These differ from the mixed tumors in that endocrine and epithelial cell constituents are present within the same cell. These findings support the hypothesis that epithelial and endocrine cells of the gut share a common cell of origin.

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Lymphocyte Gene Rearrangements—A New Technique in the Diagnosis of Lymphoma

THE HISTOPATHOLOGIC DIAGNOSIS of lymphoma can be difficult, particularly when the disease presents at extranodal sites. Conventional microscopic or immunohistochemical studies often prove inadequate for the evaluation of T-cell infiltrates, of neoplasms lacking appreciable atypia or where a superimposed inflammatory process obscures the underlying malignant process.

Recent insights into the molecular biology of lymphocytes have led to the development of a technique that provides an objective estimate of the clonal composition of lymphoid in-

filtrates. Almost all lymphomas are monoclonal populations, the progeny of a single transformed progenitor cell. Reactive infiltrates, in contrast, are polyclonal. The clonality of a lymphoid cell population can be determined by analyzing the structure of genes that code for immunoglobulins in B cells or for the antigen receptor molecules of T cells. These genes undergo precise rearrangements during lymphocyte development, assuming a different structure in each clone of lymphoid cells. By evaluating the type and number of such rearrangements in DNA extracted from a clinical biopsy specimen, the presence of any predominant B- or T-lymphocyte clone can be readily detected. When present, such clonal proliferation implies malignancy. Clonal populations constituting as few as 5% of the infiltrating cells can be shown by this method. Several researchers have shown that the pattern of gene rearrangements present in a lymphocyte population also gives evidence of its lineage (T versus B cell) and degree of differentiation.

Because cutaneous lymphoid infiltrates represent a notoriously difficult diagnostic problem, we applied this technique to a broad spectrum of such lesions. Skin biopsy specimens of mycosis fungoides, a cutaneous T-cell lymphoma, were found to contain a monoclonal T-cell infiltrate, as did the peripheral blood of patients with Sézary's syndrome, a form of chronic T-cell leukemia. Clonal T-cell proliferation has also been identified in several rare conditions whose relationship to T-cell lymphoma is controversial, such as lymphomatoid papulosis and granulomatous slack skin. This technique also permitted reliable distinction between the polyclonal lesions of cutaneous pseudolymphoma and the monoclonal infiltrates of cutaneous B-cell lymphoma. The analysis of gene rearrangements can therefore provide both scientific insights and an objective diagnostic aid in the evaluation of lymphoid cell infiltrates of the skin.

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Hodgkin's Disease—Controversies 1986

THE CELL OF ORIGIN in Hodgkin's disease remains a mystery, but recent data from a number of laboratories shed additional light on the subject. The issue is of more than academic interest because it also involves the question of the role of markers in the diagnosis of Hodgkin's disease. The morphologic diagnosis of Hodgkin's disease is relatively noncontroversial, but there is a surprising error rate in diagnosing Hodgkin's disease. A recent study found an error rate of 13%. This figure would appear to be unacceptable given the current level of therapeutic success with this disease.

The antibody Leu M1, originally defined as a myelomonocytic marker, has been increasingly utilized as a marker of Hodgkin's disease following a number of recent reports of its presence in Reed-Sternberg cells and their variants. Two major questions have arisen over these data. Weak or absent staining in cases of lymphocyte-predominant Hodgkin's disease has led some authors to conclude that this disorder is unrelated to the other forms of Hodgkin's disease. But recently Hsu and co-workers have suggested that the cells are simply more mature and as a consequence have sialylated the antigen. Using neuraminidase treatment, they removed the terminal sialic acid residues and found the antibody Leu M1 was present in most cases of lymphocyte-predominant Hodgkin's disease. The second major question concerns the specificity of the reaction. The original reports found little evidence of staining for the antibody in non-Hodgkin's lymphomas, but a recent study shows that many of the peripheral T-cell lymphomas most likely to be confused with Hodgkin's disease did stain for it.

The second question above is of practical significance. Grouping the results from all of the articles in question suggests that at least a portion of peripheral T-cell lesions contain the antibody. For those with access to frozen section or plastic section immunophenotyping, the application of standard B & T reagents can generally resolve the differential. With only paraffin blocks available, there are still some markers that will help resolve the question of peripheral T-cell lymphoma versus Hodgkin's disease. These include a number of markers commonly seen in Hodgkin's disease, but seen infrequently in T-cell lymphomas, such as HLA-DR/Ia, cathepson B, lysozyme, α_1-antitrypsin, peanut agglutinin and concanavalin A.

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Monitoring Cervical Carcinoma With Fine-Needle Aspiration Biopsy

DESPITE MAJOR ADVANCES in diagnosis and treatment, cervical carcinoma continues to be a disease of major epidemiologic importance, with an estimated 16,000 new cases each year and an annual mortality of 7,000. Rational surgical or radiotherapeutic treatment of invasive cervical carcinoma depends on accurate initial staging and subsequent surveillance for occult persistent and recurrent disease. Most recurrences occur early and in areas palpable by pelvic examination. If disease has not spread beyond the central pelvis, pelvic exenteration can offer long-term survival, even in women with recurrent cervical carcinoma. Follow-up of patients with cervical cancer traditionally has been by physical examination, exfoliative cytology and radiologic examinations. Recently some have advocated adding fine-needle aspiration biopsy (FNAB) to the list of procedures that may be effective in detecting persistent or recurrent disease in patients with cervical cancer.

The principal advantages of FNAB over open surgical biopsy for following patients with cervical cancer are rapid reporting of results, minimal morbidity and complications and good patient tolerance. In women with cervical carci-

noma, FNAB may be particularly useful in distinguishing between radiation fibrosis and tumor.

In our experience at San Francisco General Hospital Medical Center and the University of California, San Francisco, in utilizing FNAB to monitor patients for persistent or recurrent disease, FNAB led to definite changes in patient management for half of those whose biopsy results were abnormal. Abnormal results on FNAB can be useful in making decisions regarding chemotherapy and radiotherapy. Perhaps the most important use of the procedure is to select suitable patients for pelvic exenteration. In several of our patients considered to be candidates for exenteration, malignancy on FNAB of a lymph node outside the true pelvis led to cancellation of the procedure.

Patients with cervical cancer who have suspicious or benign findings on an FNAB specimen may require further workup. In cases wherein the initial FNAB specimen shows insufficient tissue or suspicious but not diagnostic changes, a repeat FNAB or open surgical biopsy should be done. It is also worth remembering that normal findings on a smear on FNAB does not entirely rule out the possibility of recurrent tumor; if the clinical presentation is suggestive, repeat FNABs or surgical biopsies may be appropriate for follow-up.

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Plasma Cholesterol Levels Determined by Lipoprotein Interactions With Cell Surface Receptors

PLASMA CHOLESTEROL LEVELS are regulated primarily by the activity of specific lipoprotein receptors on various cells throughout the body, but especially within hepatocytes. Lipoprotein receptors mediate the uptake and degradation of the various plasma lipoproteins. There are at least two distinct hepatic lipoprotein receptors: the apolipoprotein (apo)-B,E(LDL [low-density-lipoprotein]) receptor and the apo-E receptor, which is postulated to be the chylomicron remnant receptor. They are independently regulated and display unique ligand specificity. In addition, the apo-B,E(LDL) and the apo-E receptors differ in apparent molecular weight (130,000 and 56,000, respectively). Both receptors, however, possess a region within their amino acid sequence that is enriched in acidic amino acids (glutamate and aspartate) and that is postulated to be the ligand binding domain. The tentative identification of acidic amino acids within the receptors as being essential in mediating ligand interactions is based primarily on data showing that basic amino acids (lysine and arginine) of the ligands (apo-E and apo-B) mediate receptor binding.

The receptor binding domain of apo-E has been localized to basic amino acids in the vicinity of residues 140 to 160. Naturally occurring variants of apo-E with single amino acid substitutions in this region of the molecule are defective in their abilities to bind to the lipoprotein receptors and predispose affected persons to type III hyperlipoproteinemia. Recently it has been possible to more clearly define essential residues within this region of the apo-E molecule by using site-specific mutagenesis. A natural extension of the studies defining the receptor binding domain of apo-E has been the identification of two basic regions of apo-B that appear to mediate the interaction of this apolipoprotein with lipoprotein receptors.

Eventually it will be possible to develop a model describing ligand-receptor interactions; presumably these occur through the interaction of key acidic amino acids of the receptors with the key basic amino acids of apo-B and apo-E.

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Small-Cell Carcinoma of the Ovary With Hypercalcemia

SMALL-CELL CARCINOMA of the ovary is an unusual ovarian tumor that was once thought to be extremely rare but is now being recognized with increasing frequency. It occurs in young women, average age in the early 20s, with a range of 12 to 39 years. Approximately 50% of the cases have been associated with hypercalcemia, which is usually asymptomatic. The patients when further evaluated do not have hyperparathyroidism. The lesions grossly are gray-white, solid, with focal areas of hemorrhage and necrosis. On microscopic examination, the tumor consists of sheets of neoplastic cells with scant intervening connective tissue and scattered cystic spaces of varying sizes filled with pale eosinophilic material and lined by the tumor cells; these somewhat resemble graafian follicles. On ultrastructural examination, the cells frequently have numerous junctions and only rare microvilli on the free surfaces.

Scully originally coined the term "small cell" to distinguish this lesion from the more common poorly differentiated ovarian adenocarcinoma with which it can be confused histologically. The latter, however, occurs in an older patient population, is not usually associated with hypercalcemia and does not have such a uniformly poor prognosis. In addition, the cells in a poorly differentiated ovarian adenocarcinoma are about twice the size of the cells in a small-cell tumor. The cellular origin of this lesion is still undetermined, various experts favoring an epithelial, gonadal stromal or germ cell origin. To date, no dense core secretory granules have been reported in this lesion.

Various therapeutic modalities, including surgery, chemotherapy and radiation therapy, in different combinations have been used in these patients to no avail. Most cases have been clinically stage I-A at the time of diagnosis and, in spite of this, the prognosis is dismal, with death usually occurring

within months. This tumor needs to be recognized and separated from the more common poorly differentiated ovarian adenocarcinoma because of its poor prognosis, association with hypercalcemia, occurrence in young women and resistance to all current modes of therapy.

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Immunohistology for the Rapid Diagnosis of Viral Infections

THE DEVELOPMENT of increasingly aggressive and successful cancer therapy, the proliferation of organ transplant programs and the appearance of the acquired immunodeficiency syndrome have combined to place large numbers of immunocompromised patients at risk for potentially lethal viral infections. Fortunately, effective antiviral agents are becoming available. Their successful use, however, requires rapid and specific diagnosis.

Seroconversion is slow, intrinsically undependable in these patients and possibly irrelevant to the immediate clinical problem. Routine cultures are also slow and may merely reflect viral shedding rather than significant tissue involvement.

Pathologists' approach to the diagnosis of viral infection has traditionally been to identify characteristic cellular cytopathic effects, predominantly viral inclusions and associated alterations such as cellular enlargement, multinucleation and chromatin margination. This approach is valuable but does have disadvantages. False-negative results reversed by subsequent culture isolation may be distressingly frequent, especially with cytomegalovirus (CMV). Diagnostic cellular changes are probably absent in early infections in which the institution of therapy may be most beneficial. It is clear that viral nucleic acid and antigens are present in many cells that lack inclusions. In contrast, reactive alterations such as cellular enlargement and prominent nucleoli may produce false-positive results. Even when present, viral features may be recognizable without allowing specific virus identification, an increasingly important problem as effective antiviral agents with a narrow spectrum of activity are developed. For instance, acyclovir is eight to ten times less effective against varicella zoster virus (VZV) than against herpes simplex virus (HSV). Unfortunately, these two viruses cannot be distinguished on the basis of a Tzanck preparation or routine histologic or electron-microscopic examination.

Rapid direct identification of specific viruses through immunologic staining of tissue sections and smears has been hampered by limited antibody availability, though it has been feasible for many years. Monoclonal antibodies, some commercially available, are now making direct viral diagnosis practical. For example, we have found that the sensitivity of antibody C5 (Genetic Systems, Inc, Seattle/Syva Company, Palo Alto, California) in detecting CMV in frozen sections from open-lung biopsy specimens is essentially equal to that of culture or in situ nucleic acid hybridization. Other antibodies from these companies have been extremely valuable in the direct rapid diagnosis of VZV and HSV infections because they recognize glycoprotein antigens that withstand formalin fixation and paraffin embedding. A monoclonal antibody to the adenovirus hexon protein (C. Cepko and P. Sharp, Massachusetts Institute of Technology, Cambridge) and a polyclonal antibody to respiratory syncytial virus (Burroughs Wellcome Company, Research Triangle Park, NC) have also performed well. So many laboratories are now developing antibodies that soon all major viral pathogens will probably be directly detectable in tissue, even following routine fixation and processing.

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Chlamydia trachomatis—Diagnostic Techniques

Chlamydia trachomatis is a fastidious obligate intracellular parasite. The organism has been implicated as the causative agent in a variety of genital infections—including cervicitis, salpingitis, prostatitis and epididymitis—in upper respiratory tract infections and in conjunctivitis in infants. Chlamydia is effectively treated with antibiotics, but clinical manifestations may be nonspecific and subtle, and the organism has been difficult to detect.

Culture yields the highest detection rate with about 80% sensitivity, but culture is tedious and delays initiation of therapy. Special techniques are needed, making culture costly and not readily available in most laboratories.

Cytologic examination of secretions has proved to be an insensitive procedure for detecting *Chlamydia.* Cellular changes are generally nonspecific, leading to both false-positive and false-negative results. Adding iodine staining does not appreciably improve detection rates. Immunoperoxidase staining has recently been coupled with cytology, and results with this technique have varied. Technical difficulties with sample size, cell loss and nonspecific staining have precluded its widespread use.

Microimmunofluorescence for detecting antibody is both sensitive and specific for the organism. Special techniques, however, are required for its performance, and, like culture, microimmunofluorescence has not been available in most laboratories.

Direct fluorescent antibody staining for *Chlamydia* using fluorescein-conjugated monoclonal antibody to detect extracellular elementary bodies is probably the most promising procedure to date. The procedure can be used directly on smeared secretions or to enhance detection of the organism in culture and is both sensitive and specific for the organism. While not yet universally available, the procedure does not require sophisticated technical expertise and is inexpensive to do, making it more attractive to most laboratories.

Chlamydia trachomatis is difficult to detect. Direct fluorescent antibody staining appears to be the most promising, rapid and cost-effective technique at present, but, for any procedure to be effective, a heightened clinical awareness of the organism in high-risk populations is needed.

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Lymphoma—Correlating Morphology and Clinical Course of Disease

MAJOR CONCEPTUAL ADVANCES have recently been made regarding non-Hodgkin's lymphomas. These advances relate to a greater understanding of the immune system and the normal mechanisms of lymphocyte function. With this newly acquired knowledge, alternative classification systems for the malignant lymphomas have been proposed, based on modern immunologic concepts. New diseases have been described, and new approaches to the management of patients with lymphoma have been suggested. About 70% to 75% of lymphomas are of B-lymphoid origin, most arising from the cells that normally compose the follicular or germinal center of the node. About 20% to 30% of lymphomas are of T-lymphoid origin. In an attempt to correlate these concepts with clinical behavior, a translational tool was recently proposed, termed the "Working Formulation for Clinical Usage." In this system, lymphomas are divided into low-, intermediate- or high-grade tumors.

The low-grade lymphomas consist primarily of the follicular small-cleaved tumor (also known in the Rappaport system as nodular, poorly differentiated lymphocytic) and the lymphomas of small lymphocytes (also known as chronic lymphocytic leukemia, or well-differentiated lymphocytic lymphoma). These tumors are clinically indolent in behavior, with prolonged patient survival in spite of widely disseminated disease. Using multiagent chemotherapy, the group from Stanford has found that patients with low-grade lymphomas are not curable in the traditional sense, although they may be expected to live for five to ten years or more in the presence of active underlying lymphomatous disease. While in unusual cases a patient with localized (pathologic stage I) disease may be curable with radiation therapy, chemotherapy, consisting of single-agent alkylators or the cyclophosphamide-vincristine-prednisone regimen, is reserved for patients whose disease has become symptomatic or anatomically precarious.

The concept of prolonged survival in the presence of active disease is not valid in the lymphomas of intermediate- or high-grade type. These tumors, by natural history, are more aggressive and require intensive therapy at the time of diagnosis. Without the benefit of therapy, such patients would be expected to live less than a year. Newer regimens of multiagent chemotherapy have recently been described, however, that may result in long-term disease-free survival and possibly cure. These regimens, including the M-BACOD (methotrexate alternating with a combination of bleomycin, doxorubicin [Adriamycin], cyclophosphamide, vincristine [Oncovin] and dexamethasone) or similar therapies, have resulted in complete remission in about 60% to 70% of patients, with long-term, disease-free survival in about 50% of all treated patients. The specific details regarding optimal therapy in these patients depend on the specific subtype of disease, extent of disease and presence or absence of various prognostic indicators.

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Rectal Suction Biopsy in the Diagnosis of Congenital Megacolon

WHEN WE THINK of procedures used for either ruling in or ruling out the diagnosis of congenital megacolon (Hirschsprung's disease), biopsy of the muscularis propria of the rectum comes to mind as the procedure of choice. While muscularis biopsy is undoubtedly highly accurate, there are several drawbacks. It requires admission to hospital and general anesthesia. The operation may result in inflammation and scarring that make subsequent pullthrough operations difficult. The frozen tissue section, on which a pathologist is asked to make a pronouncement as to the presence or absence of ganglion cells, is generally of a poorer technical quality than well-fixed paraffin-embedded permanent sections. As a result, immature ganglion cells may not be recognized.

An alternative to muscularis biopsy is mucosal suction biopsy. The procedure avoids the disadvantages of muscularis biopsy in that anesthesia is unnecessary and the rectal wall is not incised. Only small fragments of mucosa and submucosa are obtained, which are fixed, embedded and stained in the routine manner.

The rationale behind this procedure is based on the fact that the submucosal (Meissner's) plexus bears a constant relationship to the myenteric (Auerbach's) plexus. During fetal development the submucosal plexus is populated by primitive neural elements that migrate from the underlying myenteric plexus. Therefore, the presence of ganglion cells in the submucosal layer assures their presence in the myenteric plexus. Their (ganglion cells) presence, no matter how immature, rules out Hirschsprung's disease.

The diagnostic accuracy of this procedure depends on the recognition of the characteristic morphology of the neural units composing the submucosal plexus and the appearance of ganglion cells in all their stages of maturity. Accuracy also depends on the adequacy of the sample obtained. There are some drawbacks to the method relating mostly to the size of the sample obtained and the failure to recognize immature ganglion cells. In my experience, however (more than 60 rectal biopsies), and that of others, the procedure has been highly accurate in determining the presence, or absence, of rectal ganglion cells. The technique may be further enhanced

by the recent successful application of the peroxidase-antiperoxidase technique for the demonstration of neuron-specific enolase in immature ganglion cells and nerve trunks in rectal suction biopsies.

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Immunohistology and In Situ Hybridization in the Diagnosis of Hepatitis B

IMMUNOHISTOLOGY AND IN SITU HYBRIDIZATION have increased our understanding of the pathogenesis of hepatitis B. Histologic examination, unlike serologic studies, reveals the cellular and subcellular distributions of viral antigens within the liver and the relationship of virally infected cells to inflammatory cells. Serologic markers of viral infection, however, are generally clinically sufficient for diagnostic purposes as well as being more readily available or economical. Immunohistologic study is done by incubating tissue sections of liver biopsies with antiserum against viral antigens such as hepatitis B surface antigen (HBsAg), hepatitis B core antigen (HBcAg) and the more recently discovered δ-antigen. The binding of the specific antiserum to virally infected cells is visualized by immunohistochemical procedures such as the immunoperoxidase technique or by immunofluorescence. HBsAg is present in the cytoplasm of infected liver cells, whereas HBcAg is predominantly, but not exclusively, located in the nuclei of hepatocytes. The δ-antigen is also primarily present in the nuclei of hepatocytes. HBsAg and HBcAg are present in proportions inverse to the amount of inflammation in infected livers. Thus, the panlobularly inflamed livers of patients with acute hepatitis B often lack immunohistologic evidence of HBsAg or HBcAg, whereas increasing amounts of these antigens are found as the inflammation decreases through the spectrum of chronic active hepatitis to chronic persistent hepatitis. In liver biopsy specimens of patients with chronic active hepatitis, HBcAg is generally present in a much larger percentage of hepatocytes than is HBsAg, although the converse may occasionally be the case. A search for both HBsAg and HBcAg will reveal one or the other antigen in at least 90% of percutaneous liver biopsy specimens from patients with serologic evidence of hepatitis B-related chronic active hepatitis. δ-Agent infection, always present in conjunction with hepatitis B, has been reported to be very common in fulminant cases of hepatitis occurring in homosexual persons and intravenous drug abusers, and immunohistology is helpful for the study of autopsy tissues when serum may no longer be available.

In situ hybridization for the detection of the hepatitis B genome may offer further insights into the pathogenesis of hepatitis B-related diseases. In situ hybridization can be done on routinely fixed and processed paraffin-embedded tissue. Labeled DNA strands that are complementary to the DNA of the hepatitis B virus are used as probes for detecting viral DNA within infected hepatocytes. Future study will elucidate the histologic relationship of the hepatitis B virus genome to actively expressed hepatitis B viral proteins and aid in the search for latent hepatitis B infection in patients with idiopathic chronic hepatitis.

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In Situ Hybridization in Diagnostic Pathology

WHEN A LESION cannot be diagnosed by routine light microscopy of hematoxylin-eosin-stained sections, a surgical pathologist turns to such ancillary techniques as special histologic stains, immunohistochemistry and electron microscopy, which often prove helpful in identifying cellular proteins, secretory products and ultrastructural features specific for the tissue type or lesion in question. The extraordinary advances in the field of molecular biology have recently rendered another cellular constituent accessible to a pathologist's scrutiny—namely, nucleic acids, the genetic material itself. Recombinant DNA technology has made available a wide variety of DNA probes that can be used to detect target genes by specifically annealing to complementary sequences of DNA or RNA. However, the standard research technique of hybridization to purified DNA on filters ("Southern blots"), using radioactive probes, presents serious time, expense and safety disadvantages for routine clinical use.

Two recent discoveries have now brought this technology into the realm of diagnostic surgical pathology: the nonradioactive labeling of DNA probes with biotinylated nucleotides and the finding that cellular DNA and RNA in tissue sections and cytologic smears remain accessible as targets for probe hybridization, even after formalin fixation and paraffin embedding. Thus, essentially all routinely processed pathologic specimens can be examined for the presence of specific nucleic acid sequences by in situ hybridization directly on a microscope slide.

Diagnostic applications thus far have focused mainly on the infectious diseases, proving most useful in cases not expressing the usual markers of infection. For example, the technique has identified hepatitis B virus DNA in cases serologically negative for surface antigen, herpesvirus DNA in ganglia during the "latent" viral state and cytomegalovirus (CMV) DNA in cells showing no CMV inclusions on routine histologic examination. Other studies have detected CMV DNA in Kaposi's sarcoma lesions, human papillomavirus DNA in cervical condylomas and dysplasias and JC virus DNA in progressive multifocal leukoencephalopathy.

In situ hybridization can also be used to quantitate changes in intracellular levels of specific messenger RNAs characteristic of certain neoplasias. For example, differential hybridization of a DNA probe complementary to thyroglobulin messenger RNA has been used to distinguish benign and malignant thyroid lesions. Also, the transcription of specific

oncogenes is known to be increased in some cancers, and the recent availability of biotinylated oncogene probes suggests exciting new applications of the technique. In this way, in situ hybridization should prove to be not only a useful diagnostic adjunct, but also a powerful tool for gaining insight into the molecular pathogenesis of many important lesions.

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Stereotactic Brain Biopsy

RECENT ADVANCES in imaging techniques (computed tomography [CT] and magnetic resonance imaging [MRI]) in localizing brain lesions have been accompanied by an increasing use of stereotactic brain biopsy as a means of diagnosis. This has great appeal. Stereotactic brain biopsy permits a tissue diagnosis on a specimen obtained without craniotomy, under local anesthesia and with very little risk. In our first 500 stereotactic biopsies, there has been one death (0.2% mortality).

Stereotactic biopsy presents a pathologist with a new kind of specimen. The typical specimen consists of two or three 1-mm^3 fragments. While the small size of the specimen is intimidating to a pathologist when first faced with it, it is usually adequate for diagnosis. The great advantage of the stereotactic biopsy specimen is that it is obtained from a predetermined CT-MRI target point within the lesion and therefore provides optimal material. This greatly differs from an open biopsy where a neurosurgeon takes tissue from the periphery of a lesion that may be difficult to localize at craniotomy.

Interpreting stereotactic biopsy requires a pathologist experienced in the technique, the neurosurgeon who did the biopsy and the CT-MRI scan. Interpretation is always done with complete knowledge of clinical and radiologic findings. A smear made from a part of the specimen is almost always the first step. The remainder of the specimen is processed depending on what the smear shows. There is usually adequate material for electron microscopy, cultures and permanent sections.

Stereotactic biopsy has proved to be extremely accurate in our hands for the diagnosis of brain neoplasms. While sampling presents an obvious problem, the diagnosis in most cases is more than adequate for decisions regarding treatment. We have had good success in differentiating between toxoplasmosis and malignant lymphoma in patients with acquired immunodeficiency syndrome who present with mass lesions. Stereotactic biopsy has been less accurate in the diagnosis of inflammatory lesions of the brain.

One of the major problems with stereotactic brain biopsy is that it is likely to be a rare procedure in all but the largest hospitals. This restricts the ability of a neurosurgeon and a pathologist to develop and maintain competence in the technique. We process two to three cases per week, which is close to the minimum number necessary to maintain expertise.

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Dysplastic Nevi

THE INCIDENCE of malignant melanoma has been increasing steadily in recent years. Much effort has been expended in improving the early diagnosis of malignant melanoma. This has become especially important in view of the nearly 100% survival in patients with thin (less than 0.76 mm) malignant melanoma lesions when compared with the 40% to 50% survival of patients with very thick (greater than 3.5 mm) lesions. On histopathologic examination, benign nevi have often been associated with and presumably are the precursors of malignant melanoma. In addition, a clinically increased number of benign nevi has been implicated as a strong risk factor for the development of malignant melanoma.

A distinctive nevus, the dysplastic nevus, has been associated with familial malignant melanoma, with a dominant mode of inheritance being postulated. In this setting, nevi tend to be numerous, numbering 25 to 75 per patient. Dysplastic nevi are often larger than other nevi, commonly measuring greater than 0.5 cm with irregular borders. The color of dysplastic nevi is variegated tan to dark brown to pink. Dysplastic nevi are most common on the trunk, but occur not uncommonly on the scalp, buttocks and breast. Although the likelihood that any individual dysplastic nevus may undergo malignant transformation is very low, patients with familial melanoma with the dysplastic nevus syndrome have a lifetime incidence of melanoma approaching 100%.

In diagnosing dysplastic nevi, the histologic criteria include nested junctional melanocytes present in an irregular pattern with horizontal bridging from one rete ridge to the next, random cytologic atypia of the melanocytes, dermal fibroplasia and dermal lymphocytic host response.

Because patients with familial melanoma and dysplastic nevi have been identified as having a high risk for malignant melanoma developing, careful follow-up of all clinically atypical pigmented lesions is undertaken. Photographic follow-up of these lesions aids in identifying lesions that have changed recently; these are then excised.

More controversial is the subject of sporadic dysplastic nevi. Epidemiologic studies are in progress to determine the risk of malignant melanoma developing in patients with one to many dysplastic nevi in a nonfamilial setting.

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A Marker for Monoclonality of T-Cell Malignancy

PATHOLOGISTS HAVE FREQUENTLY been confronted with the difficulty of establishing a definitive diagnosis of malignancy in patients with possible lymphoproliferative disorders. The presence of monoclonal surface membrane immunoglobulin and clonal rearrangements of immunoglobulin genes, even in the absence of functional gene expression, has greatly aided in the diagnosis of B-cell malignant tumors. In contrast, the lack of a clonal marker for T-cell malignancy has impaired our ability to make a definitive diagnosis in many cases and has limited our understanding of the biology and natural history of T-cell diseases.

An important development within the past two years is the discovery of a marker for monoclonality of T-cell neoplasms. T cells have been shown to have a receptor that is expressed during development. Analysis of the DNA coding for the β-chain of this receptor has shown that rearrangements of the gene occur early in T-cell development. The T-cell receptor gene is rearranged and transcribed only in T cells, including helper, suppressor and killer T cells, and is analogous to the immunoglobulin gene rearrangement occurring during B-cell differentiation. If a large enough clone of T cells is present (1% to 5%), the uniform DNA configuration of their T-cell receptor genes allows identification of the clone. Patterns of gene rearrangement, identified by Southern blot hybridization with gene probes, are used as markers to determine monoclonality or polyclonality of given T-cell proliferations.

Clonal rearrangements have been detected in diffuse aggressive peripheral T-cell lymphomas and in T-cell acute lymphoblastic leukemias and lymphoblastic lymphomas. Mycosis fungoides is a disorder in which the histologic diagnosis is often difficult. Clonal rearrangements have been reported in histologically confirmed biopsies and also in biopsy specimens of enlarged lymph nodes that were not clearly histologically involved, suggesting that clonal populations that cannot be recognized by routine histologic and immunologic methods may be detected by gene rearrangement studies. Most T-cell chronic lymphocytic leukemias also have clonal rearrangements, confirming the neoplastic nature of this disease. A nonrearranged or germ-line configuration of the T-cell receptor gene has been found in B-cell lymphomas, nonlymphoid malignant lesions and normal cells from patients with T-cell neoplasms. The existence of a clonal marker for T cells obviously has important implications for diagnosis and potentially for the prognosis of and therapy for T-cell malignant disorders.

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Human Papillomavirus Infection and Cervical Neoplasia

IN RECENT YEARS the genital human papillomaviruses (HPV) have been recognized as sexually transmitted pathogens of major epidemiologic importance and as oncogenic viruses playing a pivotal role in the pathogenesis of cervical neoplasia.

The incidence of genital HPV infection has increased more than sixfold during the past decade. More than 65% of cases occur in young men and women aged 15 to 29 years with the highest risk group in the 20- to 24-year age range. The high incidence of HPV infection in men has previously gone unrecognized because of the presence of small, subtle penile lesions, some of which are intraurethral. Examination of the penis with a colposcope or magnifying glass after washing with a dilute solution of 3% acetic acid will enhance clinical recognition. Spread of the HPV epidemic (estimated to affect some 2 million persons in the United States) needs to be controlled by effective treatment of the infected persons and their sexual partners.

In women, HPV frequently affects the cervix and has been linked to malignant progression, particularly when acting synergistically with other carcinogens. HPV-associated cervical lesions can be divided into three clinicopathologic categories: (1) typical (either flat or acuminate) condyloma with a low risk of malignant potential, (2) cervical intraepithelial neoplasia with koilocytosis with an ill-defined, low to high risk of malignant potential and (3) cervical intraepithelial neoplasia with nearly always a high risk of malignant progression. These categories of cervical lesions can be characterized by particular HPV types, by lesional nuclear DNA content and by cytohistologic morphology. Most condylomas contain HPV of types 6 and 11 and are polyploid. Cervical intraepithelial neoplasms, in contrast, generally contain HPV types 16, 18 and 31 and are aneuploid, regardless of their maturation or grade. The cytologic and histologic hallmark of HPV infection is koilocytosis, the presence of enlarged superficial squamous epithelial cells with a perinuclear clear space and hyperchromatic enlarged or pyknotic nuclei. Other, nonspecific findings associated with HPV include hyperkeratosis, dyskeratosis, epithelial hyperplasia, mild anisocytosis, binucleation, multinucleation and giant cell formation. In condylomas, anisocytosis and cytologic atypia are most prominent in intermediate and superficial cells, and, in general, basal polarity, basal organization and maturation are intact.

Aneuploid cervical intraepithelial neoplastic lesions, on the other hand, show cellular disorientation with loss of polarity, a crowded growth pattern, pleomorphism, increased nuclear-to-cytoplasmic ratio and chromatin clumping. Morphologically abnormal mitotic figures are identified with aneuploid cervical intraepithelial neoplasms, even in those HPV-associated lesions with prominent koilocytosis. The presence of abnormal mitotic figures and nuclear chromatin abnormalities in koilocytotic lesions of the cervix is the most reliable criterion for the diagnosis of cervical intraepithelial neoplasia and for differentiation from cervical condylomas.

Therapeutic management of cervical condylomas and intraepithelial neoplasms should be based on lesion size and distribution as determined by colposcopy and is not a function of cytohistologic grade or classification.

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Dilated Cardiomyopathy—Subcellular Mechanisms of Disease

TO CLARIFY CONCEPTS about heart muscle disease, the World Health Organization and The International Society and Federation for Cardiology jointly defined cardiomyopathy as heart muscle disease of undetermined etiology. The uniform use of such classification and terminology may help clarify the multiple and complex disorders that have been included in a less restricted definition. Arguments still exist that suggest returning to the use of the term cardiomyopathy in its broadest sense, which could include the etiology of the heart muscle disease within the term. Irrespective of the classification or use of terminology, the common postmortem findings in such heart muscle disease are strikingly similar: characteristic cardiomegaly, globoid heart with left ventricular dilation and associated findings suggesting congestive heart failure.

Classifications alone do not help greatly in understanding the subcellular nature of intrinsic heart muscle disease. In similar ways, the cell biology of the failing myocardium is poorly understood. A growing body of evidence suggests progress in understanding some cell biologic and biochemical adaptive compensations in the cardiac myocytes under the influence of thyroid hormone excess or deficiency. In such conditions, alterations in thick filament function may relate closely to changes in quantity and distribution of cardiac myosin isoforms present in the cardiac myocytes.

Analogous evidence does not exist for relating myocardial contractile changes in dilated cardiomyopathy to the thick filament. An in vitro model of doxorubicin (Adriamycin) heart muscle disease has recently been created using cultured neonatal rat cardiac myocytes (CMC) in which CMC are treated with doxorubicin hydrochloride in vitro. Myocardial contractile protein synthesis was monitored with attention focused on actin, particularly α-actin, which is the isoform present in the cardiac thin microfilament.

A dose-dependent decrease in CMC protein synthesis and particularly of cardiac α-actin was seen in CMC administered micromolar doxorubicin. Lower doxorubicin concentrations did not cause this effect on cardiac α-actin synthesis. This in vitro observation may relate to the loss of contractility seen in doxorubicin-induced heart muscle disease in vivo. As sophisticated cell and molecular biologic techniques become available to cardiovascular research, the understanding of contractility defects of intrinsic heart muscle disease may rely less heavily on classification or morphologic observation and more heavily on the nature of the biochemical defect leading to the contractile failure.

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The Use of Fresh Frozen Plasma—Indications and Risks

FRESH FROZEN PLASMA is the liquid portion (200 to 250 ml) of one unit of whole blood that has been separated and frozen within six hours after donation. It contains the labile and stable components of the coagulation system, components of the complement and fibrinolytic systems, albumin, immunoglobulins and all other plasma proteins and nutrients. One ml of fresh frozen plasma contains about one unit of coagulation factor activity; each bag contains about 400 mg of fibrinogen.

During the past decade, the use of fresh frozen plasma has increased tenfold. Each year in the United States, 700,000 patients receive almost 2 million units of fresh frozen plasma, despite few established indications for its use. About 20,000 to 70,000 cases of viral hepatitis may be transmitted annually through its use. Additional risks include transmission of other infectious diseases, anaphylactoid or other allergic reactions, alloimmunization and volume overload.

In September 1984, the National Institutes of Health and the Food and Drug Administration sponsored a conference to examine the issues and increasing professional concerns about the indications, effectiveness and safety of the use of fresh frozen plasma. One conclusion was that 90% of its current use is inappropriate. Specifically, it was stressed that there is no justification for the use of fresh frozen plasma as a volume expander or as a nutritional source since safer alternative therapies exist. The following current clinical indications for use were recommended:

- Replacement of isolated factor deficiencies for factors II, V, VII, IX, X or XI when specific component therapy (factor concentrate) is neither available nor appropriate.
- Replacement of multiple coagulation factors in patients with liver disease or consumptive coagulopathies. The efficacy, however, of administering fresh frozen plasma to patients with coagulopathy related to liver disease has not been clearly defined.
- Reversal of warfarin sodium effect. Fresh frozen plasma replaces the vitamin K-dependent coagulation factors (II, VII, IX and X; proteins C and S) when anticoagulated patients are actively bleeding or require an emergency operation.
- Massive blood transfusion (greater than one blood volume within several hours). The use of fresh frozen plasma in cases of massive blood transfusion has greatly increased in the past decade, possibly due in part to a relative unavailability of whole blood. Hemorrhage in a massively transfused patient is caused more frequently by thrombocytopenia than by coagulation factor "wash-out." The use of plasma to re-

verse hemostatic disorders should be confined to those patients in whom factor deficiencies are presumed to be the principal or sole derangement. There is no evidence that its prophylactic use decreases transfusion requirements in multiply transfused patients who do not have documented coagulation defects.

- Use in antithrombin III deficiency.
- Therapy for thrombotic thrombocytopenic purpura.

In light of the recently published indications for and risks of the use of fresh frozen plasma, physicians should carefully evaluate their clinical orders for its transfusion.

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Editorials

Long-Range Planning

THESE ARE CRITICAL TIMES for physicians and for the medical profession. The future of health care and even the future role of the medical profession in health care are uncertain. It is therefore not surprising that many medical associations and specialty societies are beginning to give attention to long-range planning. However, there are few if any successful models or precedents on which to build. An added, perhaps complicating factor is that medical organizations are democratic institutions. In democratic societies the concerns of the electorate, and therefore of the leaders, are always more with the immediate present than with the unforeseeable or even the foreseeable future, and so by their very nature they tend to think and act mainly from one election to the next. Yet the order of things is such that many, if not most, of the seminal problems of our society must be dealt with over considerably longer periods of time. In any case, and for many reasons, long-range planning for medical organizations is both desirable and necessary in the very stressed world of health care in which we find ourselves, and organizational thrusts in this direction are to be heartily commended.

But, as some are finding out, long-range planning is not easy. There is no accepted framework for how to do this in medical organizations, nor is there any generally accepted consensus, even among physicians, as to just what role the profession itself should play in relation to the various powerful forces that are now at work in health care. It seems to this writer that if long-range planning for the medical profession is to be successful, it would be best at first to recognize that the social, economic and political power bases of the profession in these areas are seldom strong enough of themselves to prevail if they have to stand alone in the fray. The profession does not have the prestige in our society that it once had, and it has never itself had the dollars or the economic power, or within itself the votes needed to win single-handedly in any serious economic or political contest in health care. But it does have unique scientific, human and professional strengths that can be converted into effective technologic, social, economic and political power. Perhaps we should begin to ask ourselves the following: (1) What are the strengths or what are the powers within the medical profession that can be brought to bear in the health care arenas where these very considerable forces are at work? (2) What are the seminal issues in health care where these strengths or these powers might be significantly influential through long-range planning?

It is suggested that the roots of power for the medical profession lie in (1) its recognized competence and expertise in the art and science of medicine (that which it professes as a profession), (2) its historic and now self-proclaimed advocacy of patients' interests (and by extrapolation this includes potential patients and the public) and (3) the more recent recognition that the medical profession gains needed social, economic and political power when it works successfully with others to form groups or coalitions where there is a common interest in achieving a common goal. The seminal issues in health care are more readily identified. At the present time they are generally accepted to be (1) quality assurance in patient care, (2) access to care for those who need it and (3) cost, which of course includes ready availability of needed resources and the efficient and cost-effective use of them.

If these are indeed the sources of power and the seminal issues to be addressed, then it would seem that long-range planning for the medical profession should attempt to develop each of these inherent strengths, and then refine its expertise in their use to address the technologic, social, economic and political problems that are plaguing health care and will continue to do so for some time to come. In fact just matching these sources of professional power to the seminal issues in health care might provide a kind of needed framework for much of the long-range planning by medical organizations. In any case it should be pointed out that this suggested approach is really not so different from what physicians do all the time in caring for their patients. Espousing the science (that is, the discipline of medicine) and the art (that is, doing what they believe is right for patients) and working with others to accomplish agreed upon goals in patient care, come naturally to physicians. It should come just as naturally to the profession to do much the same thing in the technologic, social, economic and political arenas of health care.

Physicians everywhere, including those who do not yet belong to organized medicine, can be comfortable with and supportive of this sort of professional approach to complex health care problems. And it should also engender and merit the public support that will always be needed. The expertise of our profession in the art and science of caring for the sick and preventing illness is well accepted. Here the profession speaks with authority. And just as surely, no one wants a doctor who is not working in behalf of his or her patient. This too can be a source of authority. Patient advocacy by physicians is therefore firmly rooted, and affirmative advocacy by the medical profession in behalf of patients, potential patients and the health interests of the public, based on the solid foundation of its professional expertise, would surely merit approval and public support. And then in addition, there are the recent experiences with tort reform in California and Washington State which showed what can be accomplished when the profession, as such, works effectively with other groups and organizations that share, or can be persuaded that they share, an important common interest.

It would therefore appear that one important task of long-range planning for the medical profession at this time is to develop the strengths that are already inherent in the profession, and then to find ways to exercise this power effectively in the technologic, social, economic and political arenas of health care—always in the interests of patients and the public. And it goes without saying that, in the long run, what is best for patients and the public is always best for physicians and the medical profession.

MSMW

Oral Contraceptives and Thromboembolic Disease

THE ASSOCIATION between oral contraceptive use and thromboembolic disease has been known since 1961, at about the same time that these agents came into wide usage in the Western world.[1] The data suggest that oral contraceptives are responsible for about 20 cases of venous thromboembolic disease per 10,000 women users per year.[1] Most commonly these women suffer from superficial or deep vein thrombosis with or without pulmonary emboli. The risk for developing an arterial thrombotic event, such as a myocardial infarct or stroke, appears to be an order of magnitude lower.[1]

In this issue, Schneiderman and Cello report on a rare complication of oral contraceptive use—namely, intestinal ischemia with or without infarction. In all, they found 41 cases of ischemic disease in oral contraceptive users, of whom 15 experienced reversible bowel injury, while 26 suffered frank intestinal necrosis. In this latter group, eight (31%) of the patients died. Considering the fact that about 8 million American women currently use oral contraceptives,[1] it is fortunate that there is such a low risk for this serious disorder.

In one case of transient ischemia, histologic examination of mesenteric tissue showed multiple thrombi in branches of the inferior mesenteric artery. In patients with intestinal infarction, thrombi were commonly observed in either mesenteric arteries or veins. In about 65% of the cases, thrombosis occurred in the venous distribution. The observation that events may be either venous or arterial suggests that the disorder must be explained by several factors rather than one single abnormality. This follows from a large body of literature suggesting that in arterial thrombotic events, deranged platelet physiology is a major factor while in venous disorders, defects in proteinase inhibitors, particularly antithrombin III, or elevated levels of procoagulants appear to play a more important role.[1,2] Oral contraceptive users show numerous alterations in their coagulation system, including hyperaggregable platelets, elevated levels of procoagulants and decreased levels of antithrombin III.

Deranged fibrinolysis also may play a central role in the pathogenesis of thromboembolic events.[2-5] Studies suggest that patients with decreased vascular stores of tissue plasminogen activator (t-PA) are predisposed to venous thromboembolic disease. Whenever a clot forms in the adjacent lumen, t-PA is released from blood vessel walls. In the presence of fibrin as a cofactor, it rapidly activates plasminogen, which will dissolve blood clots by proteolytic digestion of the fibrin. The blood contains vast amounts of plasminogen, but vessel walls possess minimal stores of t-PA and release of this activator is clearly the rate-limiting step in fibrinolysis. Low levels of releasable vascular t-PA are genetically regulated, although factors such as smoking and exercise modulate release of this protein.[2,6]

The interrelationship of t-PA and estrogens is complex. With oral contraceptive use, t-PA levels are somewhat suppressed, and this effect may play a role in thromboembolic disease.[1,2] However, this does not appear to be a major factor in the pathogenesis of thrombosis in these women. Groups of women with a history of thromboembolic disease while using oral contraceptives have been studied. About 90% of such patients show releasable t-PA levels at least 25-fold less than normal.[2,4,5] None of these subjects used oral contraceptives for at least a year before study. Since estrogens show no residual effect on coagulation after three months of withdrawal,[1] it must be concluded that diminished vascular t-PA stores are a predisposing factor in thromboembolic disease. Most of the data indicate a strong relationship between t-PA and *venous* thromboembolic disease.[2-5] In all these reports, only six women with *arterial* thrombosis were available for study, and these women did not have low levels of vascular t-PA.[5] This is a small number of subjects, however, and probably cannot be viewed as a statistically significant sample. Other studies do suggest an association between low levels of vascular t-PA stores and myocardial infarcts[7] or strokes,[8] although neither study involved oral contraceptive users.

Recently, our laboratory has studied patients with a relatively rare disorder, atrophie blanche.[9] These persons present with recurrent skin ulceration and fibrosis. The disease appears to result from a cutaneous vasculitis, and thrombi are found in the microcirculation, including arterioles and small arteries. These patients show levels of releasable t-PA more than 25-fold less than normal, which further supports the notion that arterial thromboembolic disease may be related to low levels of vascular t-PA stores. Subsequently, we have studied a group of about 30 patients with various other forms of vasculitis (J. Jordan, MD, S.V. Pizzo, MD, PhD, unpublished data, June 1986). Here, too, we observed that patients with active disease had low levels of releasable vascular t-PA (about 20-fold less than normal).

These data suggest a model for thrombosis in women taking oral contraceptives. A number of changes develop in their coagulation system. In some, platelet alterations may predominate while in other women changes in levels of procoagulants are paramount. Depending on the extent of derangement of the hemostatic system, thrombosis will be triggered in some of these women. Most typically, a venous thromboembolic event will occur, but in a small percentage of women, arterial thrombosis results. At this point, the most important factors are a patient's defense mechanisms against clot propagation. These defense mechanisms include levels of antithrombin III and vascular stores of t-PA. In some women on an oral contraceptive regimen, antithrombin III levels may fall significantly, perhaps by as much as 20%.[2] If, in addition, a woman has inadequate stores of vascular t-PA for any of the reasons described above, she is now at high risk for a thrombotic event and for overt disease to develop. It must be emphasized that alterations in antithrombin III induced by the pill, or the predisposition to release less than normal levels of vascular t-PA, represent alterations that would not be significant unless a coagulation event has occurred since these proteins play no role in the initial thrombotic event. Hence, the hypercoagulable state in oral contraceptive users is complex and involves derangement of the coagulation system and one of its prime inhibitors in a setting of defective fibrinolysis.

While it is possible to present a model for oral contraceptive-associated thromboembolic disease, it is important to understand the limits of such a hypothesis. In theory, one might suggest a strategy for identifying women at high risk for thrombosis to develop while taking the pill. This approach would consist of measuring t-PA levels before women begin taking oral contraceptives and then measuring antithrombin

III, t-PA and procoagulant levels several months later. The problem with this approach is that hundreds of women per 10,000 users will show significant alterations in the hemostatic balance, but in only about 20 of them each year will a thromboembolic event develop. It would appear that the cost/benefit ratio would not favor such an expensive approach, which is likely to have a high false-positive index.

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It Could Be an Important First Step

AT ITS MEETING in June of this year the House of Delegates of the American Medical Association (AMA) adopted report MM of the Board of Trustees. This could prove to be an important action by the AMA. The report is the result of a careful study by the Council on Medical Service, the Council on Legislation and the Board of Trustees. It is a thoughtful proposal for financing (or refinancing) the health care of the elderly in this nation. It addresses a number of problems that must be dealt with realistically if the Medicare program is not to face almost certain fiscal and perhaps even political disaster in the years ahead.

The AMA proposal would eliminate the current Medicare program but honor the commitments already made to the elderly. To this writer the specifics of the plan are not as important as are some of the principles it embodies. It restores the original purpose of Medicare, which was to provide access to affordable high quality health care for the elderly, and to this end it would remove care for the disabled (unless elderly) and the care of end stage renal disease (ESRD) from the program except for the elderly. These needs would then be financed from some other source.

Another basic concept of the AMA proposal is that Medicare be self-funded, but in a new way. At present about four workers are taxed to support the health care of one Medicare recipient. By the middle of the next century demographic change will reduce this to only two workers, likely to be a politically unacceptable arrangement. And it has been estimated that the present program will be 1 trillion dollars in debt by the year 2010, likely to be an economically unacceptable arrangement. The AMA proposal wisely envisions a new approach. Over time, that is before the middle of the next century, the present intergenerational transfer of resources from earners to Medicare beneficiaries will be replaced by a program prefunded by the potential beneficiaries themselves through tax contributions during their own working years. This would be augmented by voluntary health individual retirement accounts (HIRAs) which would be tax free if used to cover supplemental health care expenses. The proposal would also create a new semiautonomous federal agency to administer the program. This would be somewhat on the model of the Federal Reserve Board to give it a modicum of political independence. Other provisions would take advantage of the resources of the private sector to provide the health care, and would require some reasonable fiscal participation by the beneficiaries based on their ability to pay as determined by their annual incomes. Conspicuously absent from the proposal, which otherwise seems quite comprehensive and well thought out, is any mention of utilization review or cost control. It would seem that these will be as important in any new program as they have been found to be in the program as we know it now. But the report makes no claim to be complete or final. It is only being presented at this time with the hope that it will stimulate discussion and debate, and indeed it should.

The AMA is surely to be commended for developing this imaginative and innovative proposal. It seems in many ways to be right on target. It can be viewed as affirmative action in behalf of patients and the public. One can hope that discussions with other interested parties will develop, and that in time all those with interests at stake will become involved. One can also hope that as this occurs, and some sort of agreement or consensus is reached, an effective coalition of various groups and parties at interest will come into being and thus provide the energy and resources necessary to bring about the change that by then they all will have recognized as needed and desirable. Experience would suggest that it is unlikely that the physicians of America and the AMA can do all this alone, but the proposal adopted by the House of Delegates could be an important first step. The AMA plans to encourage wide discussion of the proposal and the problems it seeks to solve, and let us all hope that this occurs.

MSMW

Pheochromocytoma

THERE is no more important and treacherous cause of hypertension to recognize and treat appropriately than pheochromocytoma since the tumor can be successfully removed in 90% of patients. If unrecognized, it will usually cause a catastrophic cardiovascular event or death. Therefore, even though pheochromocytoma is a rare cause of hypertension (probably occurring in less than 0.1% of the population with diastolic hypertension), it is extremely desirable to repeatedly expose and sensitize clinicians to the vagaries of this most exciting and fascinating "pharmacologic bomb"—a tumor whose clinical expression, often dramatic and explosive, has rightly earned it the title of "the Great Mimic."

The clinicopathologic conference in this issue is a highly valuable exercise (as were two cases of pheochromocytoma recently reported as clinicopathologic exercises in the *New England Journal of Medicine*, Case 9-1985 [1985; 312: 568-575] and Case 6-1986 [1986; 314:431-439]). Dr Rutledge's admirable discussion of the differential diagnosis and

his approach in determining the correct cause of this patient's hypertension are most instructive.

One cannot emphasize too often the simple fact that the diagnosis of pheochromocytoma has been frequently missed because it was never considered.[1] We have found that a detailed history and physical examination can be of great value in deciding which patients with sustained or paroxysmal hypertension should be screened for pheochromocytoma since approximately 95% of patients are symptomatic. A very small percentage of pheochromocytomas cause manifestations without hypertension. It is noteworthy that tumors in patients with familial pheochromocytoma not infrequently remain relatively silent and cause few if any signs or symptoms of excess circulating catecholamines.[2(p37)] Indications for screening patients for pheochromocytoma are given in Table 1.

With regard to the present case report, it was not indicated whether the patient gave a history of recurrent headaches, palpitations or generalized sweating during the year he was known to have hypertension. Since about 95% of patients with pheochromocytoma have one or a combination of these manifestations, the absence of them is good evidence against the diagnosis of pheochromocytoma. Headache, the most common symptom, occurs abruptly and may be very severe and throbbing during a paroxysm of hypertension; it subsides as the blood pressure returns toward normal. It is often accompanied by nausea and vomiting. In patients with sustained hypertension, the headaches may be severe, but usually the intensity is moderate to mild and indistinguishable from tension headache or that occasionally experienced by some patients with essential hypertension. About two thirds of patients perspire excessively. Sweating (sometimes drenching) is generalized and most profuse during or immediately following a paroxysmal attack of hypertension. Palpitations, a sense of "pounding" in the chest, is the third most common symptom and is usually accompanied by tachycardia, although reflex bradycardia may be induced by the increased blood pressure.

Hyperthermia has been occasionally noted in patients with pheochromocytoma—apparently the result of vasoconstriction and the hypermetabolism caused by excess circulating catecholamines.[3(p103)] As suggested by Dr Rutledge, the hypothermia in the patient reported may have been related to impaired thermoregulation due to the hypertensive encephalopathy. The latter was probably responsible for the patient's severe headache on the day before admission.

The coexistence of hypertrophic cardiomyopathy in a patient with pheochromocytoma is intriguing but has only rarely been previously mentioned[4(p1310)] or reported.[5] Cardiomyopathy disappeared within five months after removal of the tumor. It is interesting to speculate that a trophic effect of excess circulating catecholamines on the myocardium may have been responsible for the hypertrophic cardiomyopathy and hemodynamic dysfunction; however, the extent to which the hemodynamic effects and hypertension per se contributed to the myocardial hypertrophy cannot be assessed. In patients with a systolic murmur and cardiomegaly, the echocardiogram can establish the diagnosis of hypertrophic cardiomyopathy and prompt a physician to avoid using inappropriate drugs, such as inotropic agents, nitrates and diuretics. Although I and my colleague, Ray Gifford, Jr, MD, agree with most of the general remarks made by Dr Rutledge about pheochromocytoma, there are several points of disagreement that deserve comment. We have found no good correlation between the amount of catecholamines secreted by pheochromocytomas and the clinical and laboratory manifestations; however, the rare occurrence of hypertension alternating with hypotension has been reported in patients with predominantly epinephrine-secreting tumors. This "manic-depressive" behavior of the blood pressure should immediately suggest pheochromocytoma.[3(p98)] We are unaware of any tumors secreting only dopamine and, even in pheochromocytomas that secrete dopamine in addition to other catecholamines, our patients have been hypertensive rather than normotensive or hypotensive. The presence of diarrhea would suggest the secretion of vasoactive intestinal polypeptide by the tumor since excess circulating catecholamines inhibit peristalsis and cause constipation, sometimes severe. Rarely, diarrhea may result from the secretions (prostaglandin, serotonin, calcitonin) of a coexisting medullary thyroid carcinoma. We have not encountered hypoglycemia in patients with pheochromocytoma. This has been rarely observed only in the immediate postoperative course after tumor removal.[2(pp57,58)]

Dr Rutledge mentions that "hypotension is commonly noted with pheochromocytoma." It should be reemphasized that either paroxysmal or sustained hypertension is present in almost all patients with pheochromocytoma. Only very rarely is hypotension a manifestation. It is true, however, that "or-

TABLE 1.—*Indications for Screening Patients for Pheochromocytoma*

- Hypertension (sustained or paroxysmal) with the following
  - Symptoms and signs*
  - Group 3 or 4 retinopathy of unknown cause
  - Weight loss
  - Hyperglycemia
  - Hypermetabolism without hyperthyroidism
  - Cardiomyopathy
  - Orthostatic hypotension (without antihypertensive therapy)
- Persons with pronounced hyperlability of blood pressure
- Recurrent attacks of symptoms and signs of pheochromocytoma, even if hypertension not found
- Severe pressor response during or induced by the following
  - Anesthesia induction
  - Intubation
  - Surgery
  - Angiography
  - Parturition
  - Antihypertensive therapy
  - Factors listed under "Clinical Presentation"*
- Unexplained circulatory shock
  - During anesthesia
  - During pregnancy, delivery or in puerperium
  - During an operation or postoperatively
  - Following administration of phenothiazine drugs
- Family history of pheochromocytoma, especially in the presence of hypertension (also screen siblings and children)
- Persons with hypertension with disease or complications sometimes associated with pheochromocytoma†
- Apparent preeclampsia or eclampsia with a hyperlabile blood pressure or severe hypertension
- Transient abnormal electrocardiogram during hypertensive episodes
- X-ray evidence of a suprarenal mass

*See Tables 1 and 2, Manger et al,[2] (or see Tables 4.1 and 4.3, Manger and Gifford[3]).
†See Table 2, Manger et al.[2]

thostatic hypotension" is observed in some patients with sustained hypertension due to pheochromocytoma. This phenomenon is not, however, observed in patients who are normotensive and who have only paroxysms of hypertension. Orthostatic hypotension may result from a reduced blood volume, a decreased sympathetic reflex or a desensitization of adrenergic receptors due to excess circulating catecholamines.[2(p54)]

In the case reported, it is interesting that verapamil administration resulted in hypotension, since nifedipine (also a calcium-channel blocker) suppressed clinical symptoms and catecholamine levels in another patient with pheochromocytoma.[5] It is not surprising that intravenous administration of metoprolol caused a pronounced elevation of blood pressure since β-blockade alone, without first creating an α-blockade, may induce a hypertensive crisis in patients with pheochromocytoma.[2(p45)]

Only a small percentage of patients suspected of having pheochromocytoma actually have the disease. Even at medical centers where a large number of patients were referred for evaluation and screening for pheochromocytoma, the incidence is usually reported to be less than 1%.[3(p4)]

A preoperative diagnosis of pheochromocytoma demands the showing of elevated levels of plasma or urinary catecholamines or their metabolites. Without chemical or radiologic evidence of a tumor, an exploratory operation is not justifiable. In patients with sustained hypertension due to pheochromocytoma, levels of plasma and urinary catecholamines or their metabolites are invariably elevated. If the concentrations of plasma catecholamines are only slightly or moderately elevated ($< 2{,}000$ pg per ml), the ability of clonidine to suppress the sympathetic nervous system and reduce plasma norepinephrine to normal levels in patients with neurogenic hypertension but not in those with pheochromocytoma confers diagnostic specificity.[6]

In a very small percentage of patients with pheochromocytomas that cause paroxysmal hypertension, secretion of catecholamines occurs only periodically and the plasma and urinary catecholamines and their metabolites may be normal when the blood pressure is relatively normal. In these patients it is imperative either to obtain blood during a hypertensive period (spontaneous or provoked) or to collect urine shortly following a hypertensive episode because occasionally a preoperative diagnosis can only be made in this way. Our experience and that of our colleagues indicate that plasma catecholamine determination is an extremely reliable method of diagnosing pheochromocytoma—false-negative results are exceedingly rare.[7]

The measurement of total metanephrine (metanephrine plus normetanephrine) in a 24-hour urine specimen seems to be a most reliable method of screening because more than 95% of patients with pheochromocytoma have elevated levels. The quantitation of metanephrines is technically easier and fewer drugs interfere with this assay than with assays of catecholamines and vanillylmandelic acid.[2(p41)] A complete 24-hour urine collection is important for proper interpretation of results; severe stress should be avoided since stress may significantly elevate catecholamines and their metabolites. Abnormal elevations of catecholamines and their metabolites can be detected in "spot" (random) specimens of urine by showing an increase in the ratio of these substances to creatinine; however, we prefer a 24-hour collection. Rigid dietary restriction is unnecessary with current methods.

If a significant fraction of urinary catecholamines is epinephrine or its metabolite (metanephrine), or if a plasma epinephrine level is elevated, it is highly probable that the pheochromocytoma is in the adrenal area, although this is not invariably so. Some investigators have emphasized the value of determining both epinephrine and norepinephrine levels in plasma and urine when familial pheochromocytoma is suspected since these tumors are almost always located in the adrenal glands and usually secrete epinephrine.[2(p38)] It should also be emphasized that appropriate screening for medullary thyroid carcinoma and hyperparathyroidism be done in all patients following removal of a pheochromocytoma to exclude multiple endocrine neoplasia syndromes.

Computed tomographic (CT) scanning can identify 95% of pheochromocytomas. It is extremely accurate in showing lesions 1 cm or greater in the adrenals and 2 cm or greater in extraadrenal locations of the abdomen. When a pheochromocytoma cannot be located by CT scan of the abdomen, chest and neck, scintigraphy with ^{131}I-metaiodobenzyl guanidine—a radiopharmaceutical agent with a propensity to accumulate in pheochromocytomas—may be helpful in localizing the tumor and providing evidence of function, although results are false-negative in at least 15% of cases; only a relatively small percent of malignant pheochromocytomas may be visualized with this contrast agent.[2(p48)] If these methods fail to show the tumor site, then vena caval blood sampling may be helpful in localization.

In the past few years we have not needed angiography to localize pheochromocytomas. Most recently it has been noted that magnetic resonance imaging, although not providing the resolution of a CT scan, may be very helpful in confirming the presence of a pheochromocytoma.[8] The behavior of signal intensity observed on a magnetic resonance imaging scan appears to be characteristic of pheochromocytoma and certain other endocrine tumors.

The key to diagnosis is to think of pheochromocytoma in any patient with sustained or paroxysmal hypertension; all patients with any manifestation suggesting the presence of this tumor should be screened when the cause of hypertension is uncertain.

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Systemic *Streptococcus equi* Infection in a Horse Handler—A Case of Human Strangles

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SERIOUS INFECTIONS with group C streptococci are uncommon in humans. Of the four species in this group, *Streptococcus equisimilis* has most frequently been reported to cause infections in humans.[1] These have included bacteremia, meningitis, endocarditis and pneumonia.[2] Another species within this group, *Streptococcus equi,* is found most often in horses and is the causative agent of strangles, an acute, contagious and deadly respiratory tract disease that attacks young horses particularly and has led to devastating epidemics in stables where many horses are housed.[3] There is only one reported case of human infection with *S equi* in a woman with bacteremia who had undergone multiple grafting procedures after a radical vulvectomy for carcinoma.[4] We report a case of bacteremia and cellulitis due to *S equi* in an ostler (horse handler or caretaker).

Report of a Case

A 56-year-old man was admitted to hospital with a four-day history of increasing swelling and pain over the right side of his face. He had experienced fevers, night sweats and rigors for two days before admission. The facial swelling had begun at the angle of the right mandible and had progressed to involve the right parotid and submaxillary region. On the evening before admission the patient noted a decrease in the facial swelling but redness and swelling had spread into the neck and anterior chest area. Two weeks before admission, a dry cough developed that had not resolved at the time of admission. There was no history of previous significant illness. The patient had worked for the past 20 years as a caretaker of horses, providing them with food and water and cleaning the stables. He lived in a mobile home within 3 m (10 ft) of a stable. None of the horses at that stable had recently been ill. He smoked two packs of cigarettes per day and drank 6 to 12 beers per day.

On physical examination, the patient was disheveled but appeared in no distress. The temperature was 36.8°C (98.2°F). The right side of the face was erythematous, warm and considerably swollen from the inferior border of the right orbit encompassing the right parotid, submaxillary and mandibular regions and the right neck and suprasternal notch area where there was tender fluctuance (Figure 1). Erythema and mild induration were also noted over the anterior chest and abdomen extending to the inguinal ligaments bilaterally. There was no crepitance at any site. The patient was edentulous except for two lower incisors that were carious but not tender to percussion.

The leukocyte count was 21,200 per μl. The blood urea nitrogen level was 18 mg per dl, the creatinine was 1.5 mg per dl and the urine showed 20 erythrocytes per high power field, 10 to 15 leukocytes per high power field and no casts, with 300 mg per dl of protein. The fluctuant area over the suprasternal notch was aspirated and Gram-positive cocci in chains and Gram-negative rods were seen. Culture of the aspirate from the wound and two blood cultures grew a β-hemolytic *Streptococcus* that was sensitive to bacitracin. The organism was identified as group C by Lancefield antiserum and as *S equi* by its nonfermentation of trehalose, lactose and sorbitol. The minimal bactericidal concentration of penicillin was 0.025 μg per ml and 4 μg per ml of gentamicin. *Bacteroides oralis* and *Bacteroides melaninogenicus* grew from the wound as well.

The patient was treated with penicillin and required surgical drainage of 50 ml of purulent fluid from the fascial planes of the right side of the face. Culture of this fluid also grew *S equi*. The patient's condition gradually improved over the following two weeks and the cellulitis had resolved three weeks after admission. The creatinine level rose to 2.5 mg per dl in the first week of hospital stay but subsequently decreased to 1.2 mg per dl on discharge from the hospital. Results of the urinalysis became normal.

Comment

In young horses, strangles can be fatal and occur in epidemic form where many horses are housed. Infected horses initially are quiet and lethargic and there is fever, rhinitis and pharyngitis. Subsequently, there is swelling of cervical nodes, which can drain purulent material. Bacteremia occurs frequently, and pneumonia and meningitis can occur. The disease is transmitted by inhaled or ingested nasal discharge. The microorganisms can remain viable in contaminated feed or water troughs for weeks.[3] A carrier state exists among horses, and, in one case, a horse continued to shed *S equi* for ten months after an initial mild infection, despite being asymptomatic during that period.[5] Protection by means of immunization is incomplete[6] and yearly boosters are recommended.[7]

Our patient had worked with horses for 20 years and lived in close proximity to a stable. The portal of entry of the organism may have been through his mouth via one of his remaining incisors, which were carious. That an infection with this organism should develop in him is remarkable and suggests an overwhelming inoculum of bacteria. His upper

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Figure 1.—The patient three days after surgical drainage. **Left,** view from right side; **right,** frontal view.

respiratory tract symptom of dry cough, subsequent development of a facial cellulitis with bacteremia with *S equi* and spread of pus along fascial planes to the suprasternal notch as well as induration of the skin of his chest and abdomen to the level of the inguinal ligament are strikingly similar to the syndrome that occurs in horses and, as such, may represent the first described case of "human strangles."

Of interest also is the initial evidence (and subsequent resolution) of renal disease reflected by microscopic hematuria, pyuria and proteinuria in the presence of a rising creatinine level. The development of poststreptococcal glomerulonephritis has been associated with infections with another group C *Streptococcus, Streptococcus zooepidemicus.*[8] In this case the initial respiratory tract infection two weeks previously may have served as an immunologic stimulus for the development of nephritis. *S equi* does not produce streptolysin O; thus antistreptolysin O would be expected to be negative.

Group C streptococci are most frequently β-hemolytic on blood agar but γ- and α-hemolytic strains have been reported.[9] When β-hemolytic streptococci are isolated, many laboratories test for susceptibility to bacitracin to separate group A β-hemolytic streptococci, which are routinely sensitive to bacitracin, from other β-hemolytic streptococci. Of group C streptococci, however, 6% to 71% have been noted to be susceptible to bacitracin,[1] as was the organism in this case. Therefore, in most circumstances, testing of β-hemolytic streptococci for bacitracin susceptibility should not substitute for grouping of the organism by Lancefield antiserum.

Penicillin has been the primary antimicrobial for treating group C streptococcal infections in general. It appears that ampicillin, cephalothin sodium, chloramphenicol, clindamycin and vancomycin hydrochloride may be acceptable alternatives.[2,10] The issue of tolerance of group C streptococci to penicillin has been raised recently. In one study by Portnoy and co-workers,[11] 16 of 17 clinical isolates of group C streptococci showed a 32-fold or greater difference between minimal inhibitory and minimal bactericidal concentrations. Synergy between penicillin and gentamicin was found in all of the 17 strains. At some variance with this is the more recent study by Roylston and associates[10] that showed penicillin tolerance in only 2 of 26 cases. Nonetheless, in those situations wherein penicillin tolerance can be shown, the addition of an aminoglycoside may be advisable. In this case, the minimal bactericidal concentration was 0.025 μg per ml; thus, the patient was treated with penicillin without gentamicin in addition to surgical drainage to which the infection eventually responded.

S equi is one of four species of group C streptococci. Of the four, *S equisimilis* and *S zooepidemicus* are known to occasionally produce infection in humans. *Streptococcus dysgalactiae* affects cows and sheep and is a rare human pathogen. This is the second report of *S equi* infection in a human but the first of a syndrome resembling strangles.

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Myopathy From Surreptitious Ipecac Ingestion

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EMETINE HYDROCHLORIDE, the major alkaloid constituent of ipecac, has clinically recognized neuromuscular toxicity.[1-6] Acute and subacute to chronic toxic myopathies have been described, but reports of human biopsy specimens are uncommon.[2,4-6] In recent reports the reversibility of this uncommon toxic myopathy primarily in association with abuse of ipecac syrup has been emphasized.[3,4,6]

We studied the case of a 27-year-old woman with a history of progressive proximal muscle weakness and elevated muscle enzyme levels. Results of the muscle biopsy were abnormal and the specimen showed irregular inclusions in both type 1 and type 2 muscle fibers. It was later discovered that she had been surreptitiously ingesting large amounts of ipecac syrup for several months to lose weight. We review previous reports of ipecac myopathy, emphasizing the clinical features and findings on muscle biopsy. Clinicians should be alerted to this toxic myopathy, especially in young women with a possible eating disorder.

(Rosenberg NL, Ringel SP: Myopathy from surreptitious ipecac ingestion. West J Med 1986 Sep; 145:386-388)

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ABBREVIATIONS USED IN TEXT

ATPase = adenosine triphosphatase
CK = creatine kinase
NADH-TR = reduced form of nicotinamide-adenine dinucleotide-tetrazolium reductase
PAS = periodic acid Schiff

Report of a Case

Slowly progressive proximal muscle weakness developed in a 27-year-old woman, beginning in the arms and progressing to the legs. She also complained of pain and tenderness of her thigh muscles and had fallen numerous times. Evaluation two months after onset showed grade 3/5 proximal and 4/5 distal muscle weakness in both upper and lower extremities. No rash was present. The remainder of the findings of the physical examination was normal. Muscle enzyme levels were greatly elevated, including a serum creatine kinase (CK) level of 2,600 IU per liter (normal < 120). Results of all other laboratory tests were normal. A muscle biopsy specimen (Figure 1) showed moderate variation in fiber size and abundant, irregularly shaped, periodic acid-Schiff (PAS)-positive accumulations in both fiber types. There was some accompanying hyperactivity of the reduced form of nicotinamide-adenine dinucleotide-tetrazolium reductase (NADH-TR) and nonspecific esterase hyperactivity within the inclusions and occasional corresponding loss of myosin adenosine triphosphatase (ATPase). The vast majority of these cytoplasmic structures reacted darkly with the modified trichrome stain but a few were clear.

A roommate revealed that the patient had been surreptitiously ingesting large amounts of ipecac for several months to lose weight. The patient denied using the medication but made a remarkable recovery, with her CK level returning to normal over the ensuing month.

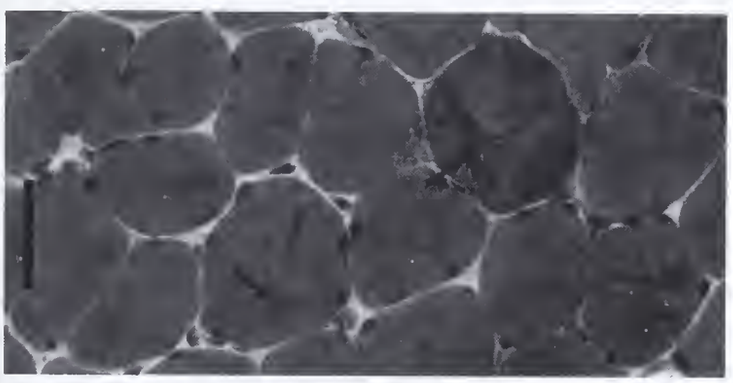

Figure 1.—A photomicrograph of a muscle biopsy specimen shows several fibers that contain irregularly shaped cytoplasmic structures **(arrows)**. Modified trichrome stain, magnification × 86. Bar = 50 microns

Discussion

This patient—and several others in recent reports of ipecac myopathy (Table 1)—most likely was suffering from bulimia, an eating disorder usually seen in adolescent girls or young women of normal weight who may have been obese before the development of bulimic episodes. To lose weight, these women willfully vomit, often by mechanical stimulation or with the use of emetics. The historical association between ingesting ipecac and the onset of muscle weakness, together with the complete resolution of weakness without treatment other than withdrawal of ipecac, is convincing evidence for this patient's myopathy being related to the toxic effects of ipecac. There was also no associated malnutrition, connective tissue disorder or family history of any neuromuscular disorder.

In experimental models of ipecac myopathy, muscle weakness and morphologic changes in muscle are seen.[7-9] The structural changes observed in our patient's muscle biopsy specimen are identical to those of other patients with ipecac myopathy and those of experimental emetine-induced myopathy. These changes consist of focal floccular loss of myosin ATPase and NADH-TR, usually PAS-positive, occasional necrotic fibers and minimal or no cellular infiltration. The severity of muscle damage depends on the dose and duration of emetine use.[7] Neuromuscular toxicity to ipecac has been reported in the treatment of amebiasis,[1,2] aversion therapy during alcohol abuse rehabilitation[5] and in patients with eating disorders.[3,4,6]

Patients who present with muscle weakness from ipecac have predominantly proximal weakness and their disorder may clinically resemble one of the idiopathic inflammatory myopathies, polymyositis or dermatomyositis.[4] Because serum muscle enzyme levels are usually elevated in both conditions and electromyography shows a "myopathic" pattern in both, muscle biopsy may be useful in distinguishing the two disorders. Most patients with inflammatory myopathies have perivascular or endomysial pleomorphic mononuclear cell infiltrates with a predominance of lymphocytes.[10] In ipecac myopathy, however, cellular infiltration is minimal or absent (Table 1). The floccular accumulation of PAS-positive material in muscle fibers appears to be characteristic of ipecac

TABLE 1.—*Summary of Reported Cases of Emetine Myopathy*

References	*Age, Years*	*Sex*	*Eating Disorder*	*Proximal Weakness*	*Muscle Enzyme Levels*	*EMG*	*Muscle Biopsy*
Fewings et al, 1973[2]	30	M	No*	Yes	Increased	ND	Muscle fiber necrosis; minimal cellular response
Brotman et al, 1981[3]	18	F	Yes	Yes	Increased	Myopathic	ND
Bennett et al, 1982[4]	19	F	Yes	Yes	Normal	Myopathic	Muscle fiber necrosis; No cellular response
Sugie et al, 1984[5]	49	F	No†	Yes	Increased	ND	Floccular-shaped inclusions
	46	F	No†	Yes	Increased	ND	Floccular-shaped inclusions
Mateer et al, 1985[6]	27	F	Yes	Yes	Normal	Myopathic	Floccular-shaped inclusions
Present Case	27	F	Yes	Yes	Increased	ND	Floccular-shaped inclusions

EMG = electromyogram, ND = not done

*Treatment for amebiasis.
†Aversion therapy for alcohol addiction rehabilitation.

myopathy and not reported in cases of inflammatory myopathies. Therefore, in a patient with proximal muscle weakness and characteristic muscle biopsy abnormalities, physicians should suspect bulimia or other eating disorders associated with ipecac abuse, even when such a history is lacking.

Addendum

Since the preparation of this manuscript, two additional cases of ipecac myopathy occurring in patients with major eating disorders have been reported.[11] Muscle biopsy was done in one patient and showed isolated necrotic fibers, amorphous eosinophilic inclusions in type 1 fibers and no inflammatory response. These cases further support the notion that in patients with binge-purge eating behavior, myopathy may develop from surreptitious ingestion of ipecac and that muscle biopsy may be useful in the diagnosis.

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Unintentional Thyrotoxicosis Factitia Due to a Diet Pill

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THYROTOXICOSIS due to the ingestion of excessive quantities of exogenous thyroid hormone is seen in persons who receive the medication as treatment for hypothyroidism, goiter or nodules (thyrotoxicosis medicamentosa) or in patients who ingest the hormone to reduce weight or because of personality disorders (thyrotoxicosis factitia).[1-4] Recently we saw several patients in whom thyrotoxicosis developed while ingesting a nonprescription capsule (Enzo-Caps) that was claimed to be "a natural food product of papaya, garlic and kelp" and was distributed as an adjunct for reducing weight. This medication was found to have been adulterated with thyroid hormones, which resulted in a form of thyrotoxicosis factitia developing.

(Braunstein GD, Koblin R, Sugawara M, et al: Unintentional thyrotoxicosis factitia due to a diet pill. West J Med 1986 Sep; 145:388-391)

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ABBREVIATIONS USED IN TEXT

HPLC = high-pressure liquid chromatography
RIA = radioimmunoassay
T_3 = triiodothyronine
T_4 = thyroxine

Reports of Cases

Case 1

In 1983 the patient, a 16-year-old girl, was found to have an enlarged thyroid (approximately 1½ times normal) without symptoms of hyperthyroidism or hypothyroidism and had normal values of thyroid function tests (Table 1, Figure 1). In early May 1984 she began taking Enzo-Caps, four tablets a day, to lose weight. About two days later she awoke with palpitations and over the next two days noted weakness, fatigue, throbbing headache and a 2.3-kg (5-lb) weight loss. She was examined in mid-May and found to have a pulse of 100 beats per minute, a normal-sized thyroid and a rapid return phase of her Achilles' tendon reflex. A triiodothyronine (T_3) radioimmunoassay (RIA) showed an elevated level, and the elevated thyroid hormone levels were confirmed at a separate laboratory (Table 1). A radioactive iodine uptake was done and showed a 6-hour value of 1% (normal 4% to 18%) and a 24-hour value of 3% (normal 8% to 33%). The patient's symptoms continued and she was reevaluated in mid-July, at which time she was again found to have a tachycardia (pulse 120), rapid Achilles' reflex and elevated thyroid hormone concentrations. During the next month, she discontinued taking the Enzo-Caps, and in mid-August she was again examined. She still complained of tachycardia and tiredness but did not have any objective findings of thyrotoxicosis on examination. Thyroid function test values were at the lower range of normal at that time (presumably because of the suppressive effects of the thyroid therapy on her pituitary thyroid axis)[5] and increased to the midnormal range when she was reexamined a week later. She reported less fatigue, improved appetite, no palpitations and was found to have a pulse of 68 and normal ankle jerks.

Case 2

This patient, the 48-year-old mother of patient 1, had received various thyroid medications in the past for "low metabolism." In 1983 she complained of fatigue and was convinced that her metabolism was abnormal. She requested thyroid hormones but her request was denied after her thyroid hormone levels were found to be normal (Table 1). At some time during the next year she began taking Enzo-Caps. She did not have any symptoms suggestive of hyperthyroidism. She accompanied her daughter to the physician's office on August 24, 1984, at which time she requested that thyroid function tests be done. A pronounced elevation in T_3 level on RIA was noted (Table 1). The patient refused further evaluation but followed medical advice to discontinue taking the

Enzo-Caps. Repeat measurement of her thyroid hormone levels four months later showed return to baseline level.

Case 3

In March 1984 a 50-year-old woman requested a thyroid evaluation because of fatigue and weight gain. Results of physical examination and tests of thyroid function (Table 1) were normal. In early September 1984, she began taking Enzo-Caps for weight reduction, and nervousness, irritability and a 2.3-kg (5-lb) weight loss occurred over the next several weeks. She was noted to have a small thyroid and a pulse of 80 beats per minute. In late September 1984, a T_3 level by RIA

TABLE 1.—*Thyroid Function Tests in Patients With Unintentional Thyrotoxicosis Factitia Due to a Diet Pill*

Patient	Date	Enzo-Caps	Lab	T_4, μg/dl	Free T_4 Index	T_3, ng/dl	Other
1	1983	No	A	9.6	3.1	...	TSH 4.9 μU/ml
	5/14/84	Yes	A	...	...	299	
	5/24/84	Yes	B	15.3	19.0	427	
	7/16/84	Yes	A	14.7	5.3	295	Free T_4 2.8
	8/17/84	No	A	6.4	1.6	...	
	8/24/84	No	A	9.4	2.7	148	Free T_4 1.08
2	1983	No	A	9.0	...	125	TSH 3.9 μU/ml
	8/24/84	Yes	A	10.2	2.7	324	Free T_4 1.34
	12/ 5/84	No	A	4.9	1.4	171	Free T_4 0.56, TSH 2.8 μU/ml
3	3/26/84	No	A	8.2	2.1	171	Free T_4 1.13
	9/28/84	Yes	A	...	...	227	
	10/31/84	Yes	A	12.8	4.4	161	Free T_4 1.8
4	1983	No	C	6.8	2.7	...	
	10/10/84	Yes	C	17.2	8.3	...	
	11/20/84	No	C	11.0	4.6	...	
5	1982	No	D	10.0	10.9	...	
	10/10/83	Yes	D	...	...	316	
	11/ 1/83	Yes	D	14.8	17.8	351	
	12/ 2/83	Yes	D	12.0	13.0	393	TSH <1μU/ml, 24-h RAIU 0%
	1/25/84	Yes	B	9.9	10.8	445	Antithyroglobulin AB +
	10/ 3/84	Yes	D	12.2	13.2	367	
	11/21/84	No	D	< 1.0	< 1.0	...	TSH 53 μU/ml
Normal Values—Laboratory			A	5.4-13.0	1.1- 4.3	100-200	TSH <10 μU/ml, free T_4 0.68-1.8
			B	5.0- 9.8	4.3-12.5	80-210	
			C	5.5-11.5	1.9- 5.2	...	
			D	5.0-13.0	5.0-13.0	100-200	TSH <10 μU/ml

RAIU = radioactive iodine uptake, T_3 = triiodothyronine, T_4 = thyroxine, TSH = thyroid-stimulating hormone

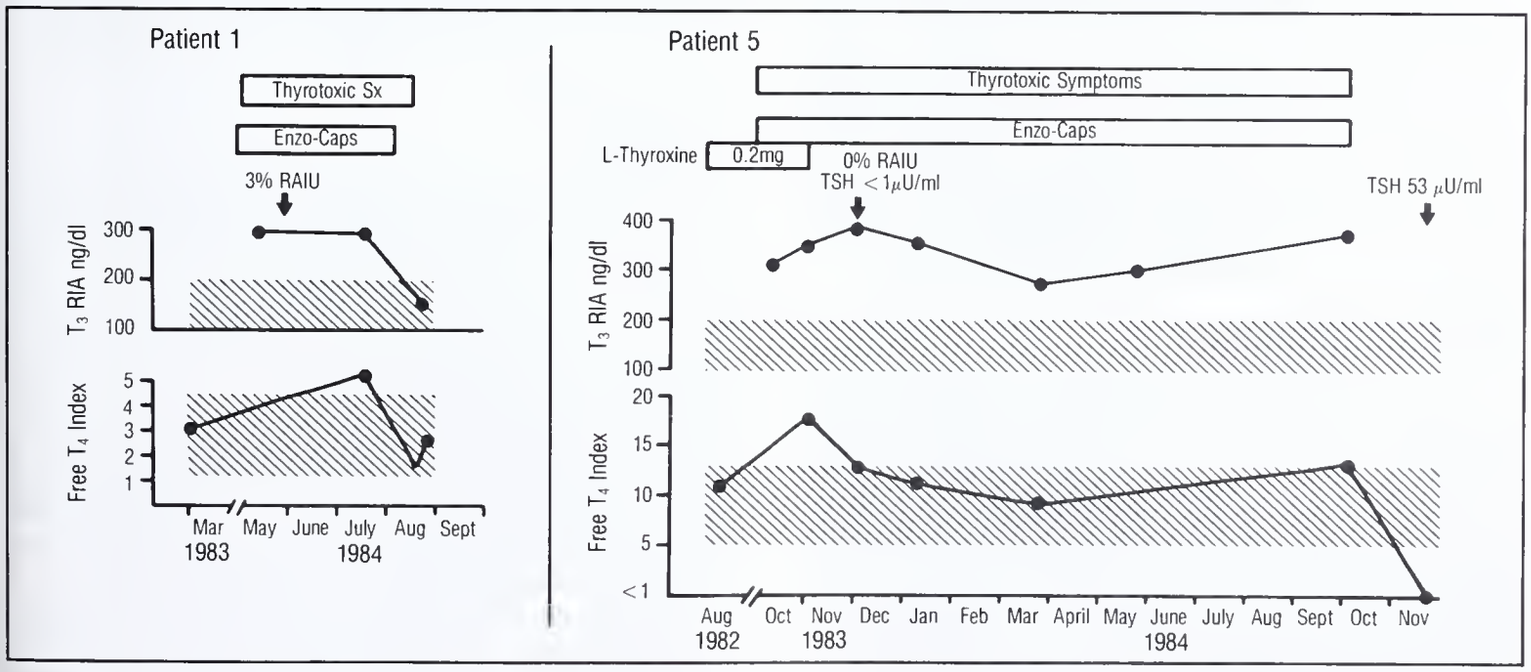

Figure 1.—Serum free thyroxine (T_4) index and triiodothyronine (T_3) radioimmunnoassay (RIA) levels in patients 1 and 5 in relation to Enzo-Caps ingestion. Hatched bars indicate normal ranges. RAIU = radioactive iodine (iodine 131) uptake at 24 h, Sx = symptoms, TSH = thyroid-stimulating hormone

was elevated. During the next month she continued to complain of irritability and nervousness and diaphoresis and tachycardia developed. She stopped taking the Enzo-Caps a few days before being reevaluated.

On examination she appeared to have mild thyrotoxicosis and a pulse rate of 100 beats per minute. Her T_3 level by RIA had decreased to normal and her thyroxine (T_4) RIA showed marginal elevation. She later noted a rapid resolution of her symptoms and did not return for repeat thyroid testing.

Case 4

A 42-year-old woman started taking 0.3 mg of levothyroxine sodium in 1973 for weight reduction. Results of periodic thyroid function tests remained within the normal range. In early 1984, she began taking Enzo-Caps, two capsules twice a day. She saw a physician in October 1984, specifically requesting a thyroid checkup, although she did not have symptoms of thyroid dysfunction. She had had a 4.5-kg (10-lb) weight loss while taking the Enzo-Caps. Her serum free T_4 index was elevated. She discontinued taking the Enzo-Caps and six weeks later her free thyroxine index had returned to normal (Table 1).

Case 5

A 54-year-old man was first seen in 1965 for an enlarged thyroid and a low serum T_4 concentration. His thyroid uptake of iodine 131 was 30% at 24 hours and antithyroid antibodies were positive. He was treated with thyroid replacement therapy. In 1982, his serum T_4 level was within the normal range with the use of 0.2 mg of levothyroxine. In late September 1983, he began taking Enzo-Caps for weight reduction, and increased sweating and a 7.3-kg (16-lb) weight loss developed. He was seen in October 1983, at which time his serum T_3 level by RIA was greatly elevated (Table 1, Figure 1). Thyroid function tests were repeated and elevations of both T_3 and T_4 levels were confirmed.

The levothyroxine therapy was discontinued in early November 1983. A month later his T_3 level by RIA was still elevated, and his thyroid ^{131}I uptake was 0% at 6 and 24 hours. The low radioactive iodine uptake, elevated T_3 level by RIA and elevated antithyroglobulin antibodies prompted a tentative diagnosis of thyroiditis (until it was realized that the Enzo-Caps contained thyroid hormone). In early October 1984, he discontinued taking the Enzo-Caps, and six weeks later he was clinically and biochemically hypothyroid. Levothyroxine replacement therapy was restarted at that time.

Materials and Methods

Seven Enzo-Caps capsules (Sicuani Laboratories, Lima, Peru) from three different persons and three tablets of desiccated thyroid, USP, 60 mg (USV Pharmaceutical Corporation, Tarrytown, NY), were obtained for biochemical analysis. The desiccated thyroid tablets were ground up and 32 mg aliquots of the tablets and capsules were digested with Pronase (Calbiochem-Behring Corporation, La Jolla, Calif) for 20 hours at 37°C by the method of Inoue and Taurog.[6] A total of 50 μl of the digested sample was extracted with 200 μl of ethanol for two hours at room temperature. The extract was dried under air and 200 μl of 0.05 mol per liter phosphate buffer, pH 7.0, was added. An aliquot was used for T_3[7] and T_4[8] radioimmunoassays. Aliquots of the ethanol extracts were also subjected to high-pressure liquid chromatography (HPLC) on an Altex HPLC with a 25-cm by 4.6-mm Ultrasphere-ODS column (Altex, Oakland, Calif) using the acetonitrile gradient method of Hearn and Hancock.[9] The fractions were analyzed in the T_3 and T_4 radioimmunoassays and the peaks compared with those found with HPLC of radioiodinated T_3 and T_4.

TABLE 2.—*Triiodothyronine (T_3) and Thyroxine (T_4) Content of Enzo-Caps and Desiccated Thyroid Tablets*

	Weight of Capsule Content, mg	T_3, μg/cap	T_4, μg/cap	T_4/T_3 Ratio
Enzo-Caps				
Source 1 . .	774	8.1	96.5	11.9
	746	9.8	98.0	10.0
2. . .	817	11.1	112.4	10.1
	679	7.9	65.1	8.3
3. . .	648	8.5	59.7	7.0
	791	8.1	71.9	8.9
	810	10.5	81.8	7.8
Mean ± SD	752 ± 66	9.1 ± 1.3	83.6 ± 19.4	9.1 ± 1.6
Desiccated Thyroid (1 grain)				
	128	6.2	50.4	8.1
	128	7.5	55.3	7.4
	127	6.4	43.9	6.8
Mean ± SD	128 ± 1	6.7 ± 0.7	50.0 ± 5.7	7.4 ± 0.6

SD = standard deviation

Results

Each of the seven Enzo-Caps capsules analyzed contained immunoreactive T_3 and T_4 (Table 2). The content of these thyroid hormones was equivalent to that found in about 60 to 120 mg of desiccated thyroid (Table 2).[10] The ratio of T_4 to T_3 in the Enzo-Caps capsules was similar to that found in desiccated thyroid. Parallelism between serial dilutions of the Enzo-Caps capsule extracts and the T_4 and T_3 standards in the respective radioimmunoassays was found. The peak elution fractions of immunoreactive T_4 and T_3 following HPLC of the Enzo-Caps extracts were identical to those found with their respective standards.

Discussion

Our patients had both clinical and biochemical evidence of thyrotoxicosis. Several complained of palpitations, weakness, fatigue, headache, diaphoresis, irritability and nervousness. The serum T_4 and T_3 levels by RIA were elevated, and, in the two patients in whom the test was done, thyroid uptake of radioactive iodine was diminished. None of the patients had goiter or specific eye signs of Graves' disease. All of the patients related the onset of their symptoms to the time they began taking Enzo-Caps, and the symptoms and biochemical abnormalities resolved following discontinuing use of the drug. That the Enzo-Caps capsules were responsible for the hyperthyroidism in these patients was unequivocally shown by direct measurement of both T_4 and T_3 in the capsules.

It is of interest that patients 2 and 5 had elevated serum levels of T_3 at a time when T_4 concentrations were normal. This pattern has been noted in patients ingesting desiccated thyroid for therapeutic purposes and may be related to the time interval between blood sampling and the preceding dose

of the hormone preparation.[11] The ratio of T_4 to T_3 in the Enzo-Caps was similar to that found in desiccated thyroid and, therefore, it is not surprising that only a T_3 elevation was found in some of the serum specimens of our patients. Thyroglobulin levels were not determined in any of our patients. Such measurements would have been useful in differentiating thyrotoxicosis factitia, which is associated with low serum thyroglobulin concentrations, from hyperthyroxinemia due to Graves' disease, thyroiditis or nodular goiter in which the thyroglobulin levels are elevated.[4]

Our patients did not fit the common psychological pattern of thyrotoxicosis factitia. They did not show the hysterical personality, dependency, emotional immaturity and rigidity that have been noted by others.[2] None of the patients were taking the medication to absolve themselves of guilt or for self-destructive motivations. All of them ingested the tablets because they believed that they were a nontoxic "natural" substance that would allow them to lose an appreciable amount of weight *"while eating your regular diet* **without** the use of drugs, appetite suppressors, starch blockers or time-consuming preparations," as advertised by the distributors of the product.

The Enzo-Caps were manufactured in Lima, Peru, and imported into the United States under the guise of a nutritional supplement for weight reduction. The labels and brochures stated that they contained papaya, garlic and kelp. The capsules could only be ordered directly from the import company and were distributed directly or through an intermediary. At the time we had discovered that the capsules contained a significant amount of thyroid hormones, the importing firm was no longer in business and the capsules were no longer available. We have since learned that in addition to thyroid, the capsules contained about 3.9 mg per capsule of diethylpropion hydrochloride (Food and Drug Administration analysis, sample number 84-351-969, October 9, 1984) and 21 mg per capsule of hydrochlorothiazide (analyzed by Shankman Laboratories, Los Angeles, January 14, 1985, and provided by Stan Solomonson, DC, Los Angeles). Thus, these capsules illegally contained a combination of potent thyroid hormones, a sympathomimetic agent and a diuretic; each of these agents may have been responsible for the patients' symptoms.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Physician Awareness of Developmental Disabilities

TO THE EDITOR: I wish to express my enthusiastic support for the June 1986 article entitled "Current Issues In Developmental Disabilities."[1] I have a great interest in the particular families who are dealing with such disability. In the little city of Las Cruces, New Mexico, (60,000 people) we have at least 6,000 of these families, which would fit with the national statistics of 10% of the population being disabled. Your article on developmental disabilities, therefore, shows just the tip of the iceberg. There are many other disabilities with which we as physicians feel equally frustrated, unfamiliar with the causes and nature of the disabilities and the problems entailed.

I really believe that as more articles like the one in the June issue reach our awareness, there will be a push for continuing medical education and medical school training to begin to deal with these people and with the issues that they face daily and to help us be a little more responsible in our dealing with them. Again sincere thanks for bringing this article to the physicians of the west and southwest.

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REFERENCE

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Tetracycline-Resistant *Neisseria gonorrhoeae*

TO THE EDITOR: We would like to report isolation of two strains of plasmid-mediated tetracycline-resistant *Neisseria gonorrhoeae* in the state of California.

Two patients presented for treatment of dysuria and urethral discharge at the Naval Hospital, San Diego. The illnesses were locally acquired within San Diego County, and no epidemiologic links between the two cases were found. Both patients were treated with aqueous penicillin injection, 4.8 million U (APPG).

Disc sensitivity testing to penicillin and tetracycline were performed at the Naval Hospital using the modified Kirby-Bauer method.[1] Both isolates were found to be resistant to tetracycline and sensitive to penicillin. Further testing at the Centers for Disease Control (CDC) using the agar dilution method[2] of determining minimum inhibitory concentrations (MIC) confirmed these results, with the MIC to tetracycline being 32 μg per ml. Both organisms contained 2.6 and 25.2 megadalton plasmids, similar to organisms with plasmid-mediated high level tetracycline resistance that have been recently described.[3,4]

In the United States, tetracycline resistance in *N gonorrhoeae* has been usually chromosomal mediated and has frequently been associated with chromosomally-mediated resistance to penicillin,[5] and with penicillin resistance due to β-lactamase production.[6] The first reports of high-level tetracycline resistance in *N gonorrhoeae* were published in September 1985. To date there have been 79 isolates confirmed by CDC and unconfirmed reports of others. Although the patients in this report were treated with penicillin, to which these strains are susceptible, and were presumably cured, the appearence of these isolates in California is evidence of the rapid nationwide spread of this organism. We wish to reemphasize the CDC recommendations published in the 1985 *STD Treatment Guidelines*[7] that tetracycline alone should not be used as therapy for gonorrhea.

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Physicians' Obligations in Legal Matters

To the Editor: In California, Proposition 51 with its limitations on jury awards to the symptomatic-only disability is now a reality. I have heard many sighs of relief and hopes that many of our problems are now solved, yet all of the medical profession is holding its breath awaiting the next "attack" by the legal profession.

Now is not the time to sit back and wait but to look closely at some of our own shortcomings. Recently I experienced a situation in which a colleague, from whom I had requested a consultation for a difficult problem, lectured my patient on his own steadfast determination to resist subpoena if the patient's attorney involved him in her litigation. As orthopedic surgeons both of us realize that the treatment of trauma carries the possibility of litigation with each case. My consultant had been informed of this risk beforehand and had agreed to consult.

This example is not unique and most physicians do not wish to "become involved." Such attitudes leave a vacuum in our legal system that is filled very handily by the physician or surgeon who is "specializing in medicolegal reports." Such physicians may have had limited clinical experience, medical or surgical, and for many it can be an easy source of income. That physician who is engaged in a busy practice, who keeps abreast of modern technique and teaching and who has the practical experience and determination to accurately diagnose a problem simply does not have the time, let alone the inclination to become involved in legal matters. Many plaintiffs and defendants therefore get opinions that may lack this maximum effort and expertise.

May I therefore submit that the medical profession has a duty, even a moral obligation to assist the courts in dispensing equity? California's voting population has issued a mandate to alter the legal consideration of "pain and suffering" and it now remains for the medical profession to take responsibility in adding accurate objectivity to this mechanism. In the 1950s New York State developed a pattern in establishing an expert medical witness panel responsible only to the courts. Such a program allowed the physician to be accurate and unbiased. An attempt to implement this concept in Sacramento County, California, failed due to plaintiff legal opposition. The California Medical Association and local societies could now come forth and establish similar panels. The time is optimal, there is a need, but the medical profession must step out of its cocoon of legal isolationism and each of us be willing to cooperate in such a plan. Proposition 51 will thus achieve its goal.

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AFP Anxiety

To the Editor: Based on our experience in California with a new screening modality, we believe society has created a new form of mental anguish: AFP anxiety. We have seen severe psychologic and physiologic disturbances in patients and family members after a "positive" result is reported from maternal serum in the California Alpha Fetoprotein Screening Program. A recent report in the public health literature warned us that, despite our efforts in education, women would have substantial gaps in their understanding of the test.[1] In our experience, this is especially true in dealing with the relatively large number of "false positive" results. Furthermore, this anxiety is only partially relieved when the repeat blood test or amniocentesis is "negative," in that a normal baby cannot be assured with 100% certainty. We cannot even prescribe anxiolytics in this case since the prototype drug has been associated with a number of congenital abnormalities when used in pregnancy.[2]

We are not fond of delivering anencephalic babies, but we also hate to see such intense anxiety in our pregnant patients. Most women with "positive" results in the AFP screening go on to have normal babies. The California Alpha Fetoprotein Program is doing more harm than good and should either be altered to prevent "AFP anxiety" or abolished altogether.

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Plague

To the Editor: In the article on plague in the April issue,[1] there are a number of errors, some of which may adversely affect diagnosis or treatment of plague patients and their contacts.

Risk Factors for Acquisition

Although plague remains a rare disease in the United States, more than half of all human plague cases in this country occur in sparsely populated New Mexico. It was stated in the April article that humans at greatest risk of acquiring plague are those with extensive contact with wild or domestic animals, specifically hunters, trappers, farmers and veterinarians. Although cases of plague have occurred in these occupational or avocational groups, in New Mexico the greatest risk factor for acquiring plague is residence in a rural area. In the period 1980 through 1985, there were 84 cases of human plague reported in New Mexico. Of the 84 persons, only ten (12%) acquired plague as a result of hunting or trapping and seven (8%) probably became infected pursuing recreational activities (hiking, camping and picnicking). Sixty-seven persons (80%) became infected in or near their home or place of work either as a result of being exposed to plague-infected fleas from epizootics nearby or by passive transport of fleas into the home by pet dogs and cats. Physicians practicing in areas with enzootic plague should consider plague in the differential diagnosis of fever with lymphadenopathy in all persons, not just those with obvious exposure to animals.

Diagnosis

The discussion of laboratory diagnosis failed to mention fluorescent antibody (FA) staining of lymph node aspirate material among the tests readily available to clinicians for diagnosis of plague. FA staining is both sensitive and specific and is clearly a better method for making the presumptive diagnosis of plague than Gram's stain. FA testing is available, usually on a same day basis, at state health department labora-

tories in Arizona, California, New Mexico, Oregon and Washington and at some Indian Health Service Hospitals. State health departments in other states can arrange FA testing at the Centers for Disease Control. We urge physicians caring for persons suspected to have plague to consult with their state health department as soon as the diagnosis is considered. This will facilitate diagnosis and allow for early public health action to prevent additional cases.

Survival Rate

The reference cited[2] in the April article and our own data do not support the 10% survival rate given for plague pneumonia. In New Mexico there have been 171 human cases reported to date. Eighteen (11%) cases were recognized with secondary plague pneumonia; six (33%) survived and poor survival was usually a result of delayed recognition of the etiologic agent. Pneumonic plague does respond to appropriate antimicrobial therapy and is not necessarily fatal.

Prevention

In the article, chemoprophylaxis was recommended for asymptomatic household contacts of both bubonic and pneumonic plague cases. The rare situation of co-primary cases within a household was cited as the basis for this recommendation. However, these clusters represented exposure to the same environmental risk factors and not person-to-person spread. Because of the potential for airborne transmission, abortive antibiotic therapy is indicated for face-to-face contacts of patients with plague pneumonia. Similar therapy for household contacts of bubonic plague cases is usually unwarranted and should be decided on a case-by-case basis. Because of the importance of the environment, when the illness is acquired near home, we encourage local pest control measures for all residents in the area.

History

It was stated that the largest and most recent epidemic of plague in the United States occurred in San Francisco in 1901. This outbreak was the largest but there have been two subsequent outbreaks: Oakland, California, in 1919 and Los Angeles, in 1924.[3]

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Dr Ganem Responds

To the Editor: Dr Hull and his associates raise a number of useful points about the diagnosis and prognosis of plague, none of which importantly contradicts the substance of the points made in the April review.[1] As regards risk factors for acquisition, the importance of proximity to the animal reservoir is clearly stressed, and the list of specific occupational risk factors is explicitly indicated as illustrative rather than exhaustive (p 447). The specific circumstance of transmission from the wild animal reservoir to the home via pets was likewise noted (p 450).

I agree that fluorescent antibody testing of aspirates is likely to be superior to Gram stain when it can be carried out in a timely fashion; the virtue of the Gram stain is, of course, its immediate and universal availability, virtues not shared by any serologic test. All of us would, I am sure, agree that empiric therapy should be instituted on clinical and epidemiologic grounds without delay. As regards prophylaxis, the recommendations of Hull, Torok and Brown for pneumonic plague are identical to those set forward in the review. The issue of prophylaxis of bubonic plague contacts is obviously less straightforward: the relative infrequency of cases in household contacts was pointed out (p 450), but the more conservative practice of broader prophylaxis was advocated, as in other recent writings on the subject,[2] given the low risk and cost of this maneuver and the vagaries inherent in determining the sources of infection in any individual case.

Lastly, I am grateful to the authors for providing their latest mortality data and for amending my historical account by pointing out the Oakland and Los Angeles plague outbreaks.

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Correction: The Arizona Health Care Cost Containment System

To the Editor: My article on the Arizona Health Care Cost Containment System in the July issue[1] contains a typesetting error on page 117 under the heading "Quality." The sentence "The inclusion of indigents has not occurred" should read "The inclusion of *non*indigents has not occurred." (Or perhaps better, "Nonindigents have not elected to join any of the plans.")

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REFERENCE

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Radiologic Case

Right Upper Quadrant Pain

JONATHAN M. LEVY, MD; SAMUEL J. HESSEL, MD, *and* RICHARD M. SPIEGEL, MD, *Scottsdale, Arizona*

A 40-year-old man, a dentist, complained of right upper quadrant pain. An ultrasound examination of his gall bladder showed no abnormalities but an echogenic mass was found in the right kidney (Figure 1). A computed tomographic (CT) scan (Figure 2) showed the mass to be of low density (−60 Hounsfield units).

What is the diagnosis?

What would you do with this patient?

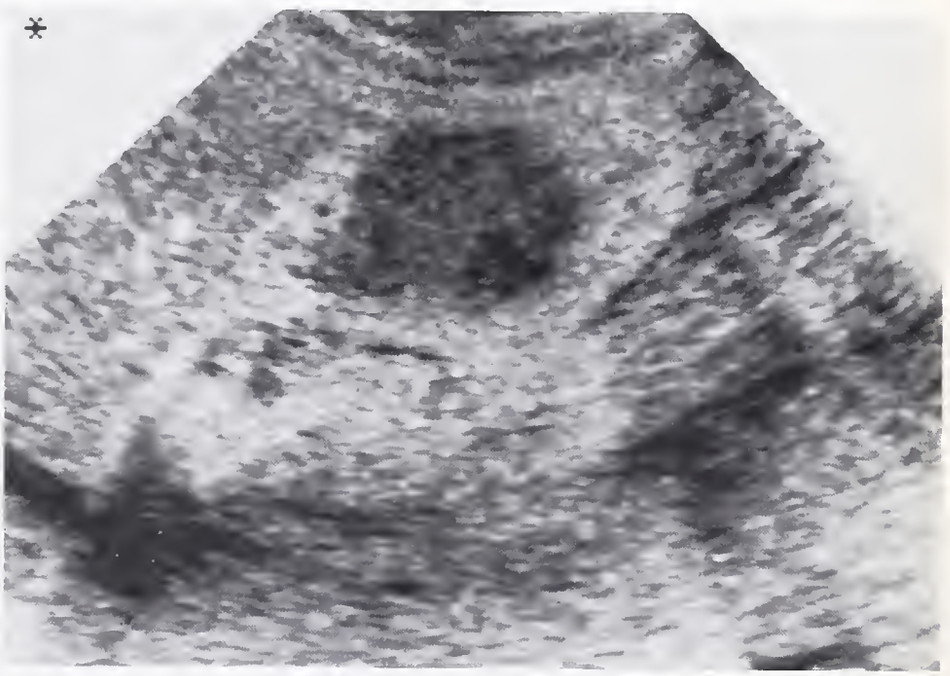

Figure 1.—Ultrasound of right kidney shows echodense mass.

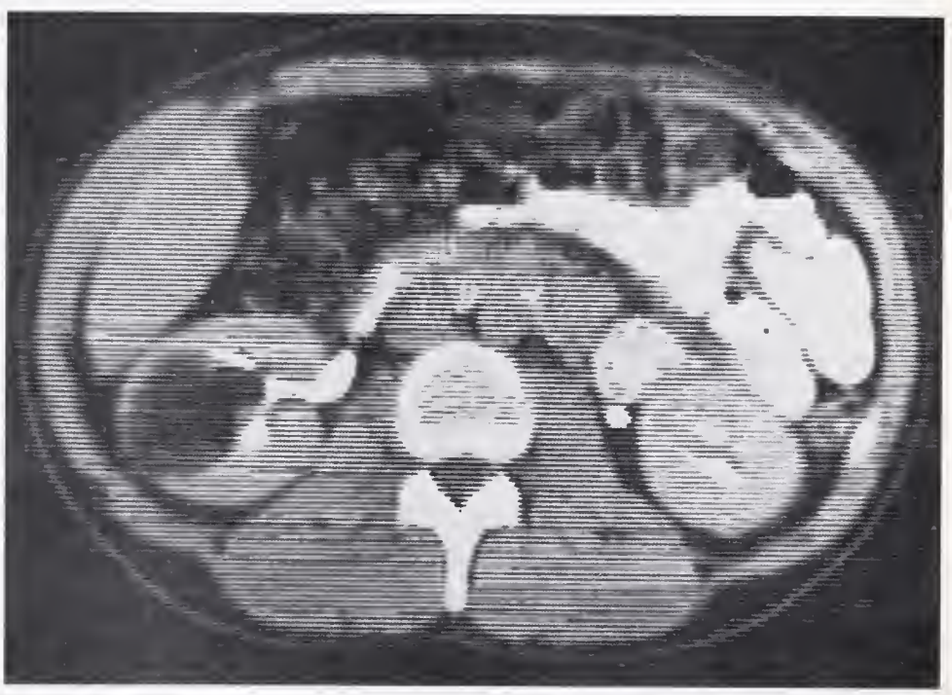

Figure 2.—CT scan of the abdomen, showing low attenuation mass in the right kidney.

(Levy JM, Hessel SJ, Spiegel RM: Right upper quadrant pain [Radiologic Case]. West J Med 1986 Sep; 145:395-396)

From the Department of Diagnostic Radiology, Scottsdale Memorial Hospital, Scottsdale, Arizona.
Reprint requests to Jonathan M. Levy, MD, Department of Diagnostic Radiology, Scottsdale Memorial Hospital, 7400 E Osborn Road, Scottsdale, AZ 85251.

Answer: Angiomyolipoma of the kidney.

Angiomyolipoma is a relatively uncommon benign renal tumor, composed of blood vessels, smooth muscle and fat in varying proportions. There is an approximate 80% incidence of angiomyolipoma in patients with tuberous sclerosis; in this disease, the masses are usually multiple and bilateral. Single tumors are not associated with any other disease process and are more common in women than men. Since the advent of CT and ultrasound, these tumors are being discovered with increasing frequency, usually as an incidental finding in the course of abdominal imaging. While angiomyolipomas represent 1% of resected renal tumors, they are present in as many as 11% of kidneys studied at autopsy.

The typical appearance of angiomyolipoma on ultrasound is that of an echodense mass (Figure 1). Many other entities, however, can produce echogenic masses in the kidney. These include renal carcinoma, lymphoma, oncocytoma, infarcts and renal sinus lipomatosis. The identification of fat in a renal mass on CT (Figure 2), however, is a very specific finding and essentially excludes all of the other lesions. In this patient, therefore, the diagnosis could be made with confidence. Percutaneous biopsy for confirmation may be nonspecific because fat is present in the normal renal sinus.

Though most angiomyolipomas are now found incidentally, they are potentially capable of producing serious morbidity. Patients may present with flank pain or shock due to hemorrhage into the tumor or retroperitoneum, a relatively common occurrence because of the abnormal, florid vascularity of the tumor. In patients with tuberous sclerosis, destruction of renal parenchyma by multiple lesions may lead to renal failure.

Treatment of renal angiomyolipoma has historically been surgical. Small, incidentally discovered tumors can probably be followed, as they often remain stable on serial ultrasound examinations. Larger tumors can be resected without nephrectomy, especially if significant hemorrhage has not occurred. Transcatheter embolization can also be considered for treatment of hemorrhage. Our patient, when presented with the options, chose to be followed without surgical treatment.

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Topics in Primary Care Medicine

Practical Management of Demented Elderly

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
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Series' Editors

An estimated 4 million Americans currently suffer from dementia. A third of these are so severely affected that they need assistance with basic activities of daily living. Nursing-home care, necessary during the later phases of the illness or when no family is available, is inordinately expensive. Thus, the cost in economic, social and psychological terms to demented patients and their families is almost incalculable.

Practitioners will increasingly be faced with issues of diagnosis and management of dementia and its consequences. Many excellent texts and journal articles have reviewed the diagnostic process necessary to confirm the presence of dementia and to look for potentially reversible causes. Cognitive impairment may accompany major medical illness, depression, psychotic disorders and toxic or metabolic disturbances as well as the dementias, and these must be carefully distinguished. Dementias are characterized by multiple deficits, including memory loss, visual spatial disorientation, language dysfunction, poor abstraction and mathematical skills and personality changes. They present with a history of chronic, progressive deterioration. The two major types of nonreversible dementia are Alzheimer's disease, accounting for as many as 70% of cases, and multi-infarct dementia, accounting for about 20% of cases. Overall, about 20% of all elderly presenting with dementia will have a reversible or partially reversible cause identified. Of these, less than half will actually be restored to normal mental function with treatment.

Most patients with dementia will require ongoing care, coordinated by a primary physician. Effective management requires medical skills, assessment of social and psychological needs of patients and their families and the coordination of supportive services.

Medical Management

All concurrent medical problems must be reviewed periodically. Regular office visits for reassessment are preferable to waiting for problems to become unmanageable. The frequency of such visits should be according to each patient's needs, but even in the most stable situations should not exceed four to six months. All medications, both prescription and nonprescription, should be reviewed at each visit, especially those that may impair alertness and cognition. If possible, a responsible party should bring all medications to the office. Routine medical screening procedures, such as blood pressure determination and breast, rectal and pelvic examinations, should not be neglected. Early detection of medical problems may prevent premature deterioration of these patients and their confinement to an institution.

Decisions regarding invasive diagnostic or therapeutic procedures must obviously be individualized. The process of obtaining informed consent is altered in the case of demented patients. When enough cognitive function remains that the patient can comprehend the choices being offered, even if in simplified language, the sense of personal integrity can be maintained and assent given. When a patient is unable to participate in decision making, a physician must, in making decisions, incorporate advance directives if available, the best interests of the patient and the wishes of family members. In many cases there is no family to assist in making decisions, and the process of obtaining a court-appointed conservator is lengthy. A physician may face critical decisions before such a process is completed. It is important, therefore, to begin thinking about such problems early in the course of a dementing illness and discuss them frankly with patients. Rather than being affronted, most patients see the opportunity to discuss these issues as a way of maintaining control over their futures.

The mental state of a patient should be periodically reevaluated. Specific areas of loss, such as language disorders, spatial disorientation, memory loss, mood disturbances and behavioral problems, should be monitored. Many tests of cognitive function are available, including the Folstein Mini Mental Status Examination and Pfeiffer's Short Portable

(Heikoff LE: Practical management of demented elderly. West J Med 1986 Sep; 145:397-399)

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Mental Status Questionnaire. These are useful for initial screening and subsequent monitoring of changes. If there is a question about the accuracy of diagnosis or presence of concurrent psychiatric problems, more detailed neuropsychiatric testing may be of help. Such testing is best done by a neurologist or psychologist experienced in its administration and interpretation, especially in the elderly.

Differentiating depression from dementia can be very difficult. Features that support the presence of depression include a precise rather than gradual onset of symptoms, rapid deterioration, heightened patient awareness and distress over deficits, wide variability in performance on tests of similar difficulty and frequent "I don't know" answers rather than inaccurate guesses. Psychomotor retardation, insomnia and loss of appetite may be present. Consultation with a psychiatrist may be appropriate. When the diagnosis remains unclear and there are no contraindications, a trial of antidepressant therapy can be initiated. A drug with minimal sedative and anticholinergic side effects, such as desipramine hydrochloride, should be started at low doses, that is, 10 to 25 mg at bedtime. The dose can be increased by 10 to 25 mg each week and its use should be discontinued if side effects occur or a dose of 150 mg is reached without therapeutic effect. One can expect improvement in mood, appetite and ability to carry on activities of daily living, but dramatic changes in cognition are uncommon.

Paranoid ideation, hallucinations and disruptive or hostile behavior may respond to the use of the major tranquilizers. The chlorpromazine-thioridazine group, which provides greater sedation, is useful in patients who are agitated or who wander. The starting dose of thioridazine hydrochloride is 10 to 25 mg at bedtime. Mesoridazine besylate is a related drug used in the same doses. These agents have fewer extrapyramidal side effects but more hypotension and anticholinergic side effects as compared with the butyrophenones. Haloperidol is minimally sedating and may be preferred in patients with paranoia and hallucinations. Therapy should be started at low doses—that is, 0.5 mg to 1 mg once or twice a day—and increased by 1 mg per day every few days until control of target symptoms is achieved or undesirable side effects occur. Careful management of these behavioral problems will make life for a patient and the patient's caregiver easier and may delay or prevent institutionalization and "caregiver burnout."

Hearing and visual problems must be screened for and corrected when possible. Sensory deprivation can significantly worsen cognitive function and increase physical dependency in an already impaired person.

A person's nutritional state also requires specific periodic assessment. Despite initially normal serum albumin and vitamin levels at the time of a "dementia work-up," nutrition may deteriorate due to declining social and physical skills. Alcohol intake must be monitored. The condition of a patient's dentition should be included in the evaluation of the patient's nutritional state. When dental work is needed, close communication should be maintained between physician and dentist to avoid complications, particularly those related to central nervous system-active drugs.

Urinary incontinence is a common problem in demented elderly. The degenerative central nervous system process itself may cause an uninhibited bladder, also called detrusor instability. A patient cannot delay voiding until reaching the bathroom. A careful history and physical examination should be done to look for treatable causes, such as urinary tract infection, atrophic urethritis, prolapse causing stress incontinence, prostatic hypertrophy or side effects of medications resulting in overflow incontinence. The use of regular toileting schedules and specific drug therapies can eliminate or reduce incontinence. The diagnosis and treatment of incontinence in the elderly have been described in several recent reviews. Anticholinergic drugs can worsen cognitive function and should be avoided if possible. Smooth muscle relaxants, such as flavoxate (300 to 800 mg per day) or calcium channel blockers, may be effective. The use of imipramine appears to affect bladder function in several ways and the drug is well tolerated at doses of 10 to 25 mg three or four times a day. Its major side effect is orthostatic hypotension. If incontinence persists despite treatment, or side effects prove intolerable, incontinence pants are preferable to long-term catheterization.

Functional Assessment

The functional assessment of a demented patient focuses on the ability to carry out specific daily tasks rather than on diagnoses. The functional assessment includes evaluating activities of daily living such as feeding, bathing, dressing and toileting and instrumental activities of daily living—shopping, cooking, housekeeping and money handling—and the extent of formal and informal support systems. Many assessment instruments are available to document these functions, and such tools are useful for periodic comparisons of a person's progress. The Pfeiffer Functional Assessment Inventory has sections for evaluating activities of daily living and instrumental activities of daily living and was designed for outpatient use. It is not necessary, however, to use these instruments in practice as long as each function is described sufficiently that the practitioner understands how the patient is managing on a day-to-day basis.

When new functional difficulties arise, a physician must look for contributing medical, social and psychological problems, rather than assuming the change is due to progression of the underlying disease. For example, suppose a mildly demented patient who lives alone becomes unable to manage cash and shop for groceries in a local store. The clinician must consider the possible contributions of a new visual problem, a decline in mobility due to a flare of arthritis, loss of a neighbor who provided assistance or progressive decline of memory and arithmetic skills due to the underlying dementing illness. More than one process can occur simultaneously, and a primary care provider must dissect out those that may be reversible.

The safety of a patient's home should be reviewed. In-home occupational therapy evaluations can be extremely helpful in this regard. Specific modifications may be necessary to permit a longer period of independent living. Latches and locks may prevent wandering. Valves to turn off the stove may allow the patient to be unattended. Hand rails, tub chairs, elevated toilet seats or smoke alarms may be required. The roles of neighbors, family and friends in providing an "informal support system" must be determined. Formal supports, such as Meals on Wheels, Adult Day Health programs and the like may also be involved. Good communication between the physician and all other providers is essential. All

too often a patient's primary physician is unaware of services performed by other caregivers. Support services vary widely and depend on the size and resources of a local community. They can include senior companion visitor programs, escort services, in-home arts programs, delivered hot meals, senior centers with meals, adult day health centers, home care nursing and medical services, attendant care services and financial management assistance programs. When there is no family member to organize such services, case management may be indicated. A case manager may be a nurse, social worker or trained paraprofessional who coordinates formal and informal support systems for the patient. Such services may be available through Jewish Family Services and Catholic Social Services in some communities and through some home health agencies. The county social service department usually can suggest available services in each community.

Alternatives to independent living include residential care homes and residential hotels. The level of supervision varies from place to place, but often these alternatives can delay or prevent nursing home placement. Clearly a good working relationship between physicians, social workers and occupational and physical therapists is crucial to adequately assess function and provide the least restrictive living situation for a demented patient.

Family Education and Support

Another important role of the primary care physician is to provide information and support to the families and friends of demented persons. As Alzheimer's disease receives increasing attention from the media, the public's awareness and concern have greatly expanded. Families may have questions about prognosis, treatments they may have heard or read about and the genetic implications of the disease. While the genetics of Alzheimer's disease is not completely understood, the number of families with a true autosomal dominant pattern of inheritance appears small. However, the first degree of relatives of a patient with Alzheimer's disease may have a severalfold increased risk compared with the population at large. Prognosis is an even more difficult issue to address because the rate of deterioration varies considerably and will be affected by concurrent social and medical events. It is important to reassure families of the physician's continued interest and desire to maximize function at all stages of the disease.

Referral to a support group may be useful. The Alzheimer's Disease and Related Disorders Association (ADRDA) is a national organization with chapters in many communities, offering educational programs, legal and financial counseling and group support programs. The sharing of problems and practical solutions with other families is of enormous benefit.

Several books address the day-to-day needs of demented patients and their families and make practical suggestions for household organization, financial management and psychological problems. One of the most popular is listed in the references. In individual circumstances, psychiatric or psychological counseling may be necessary for one or more family members. Old family conflicts resurface and interactions between parents, children and siblings all undergo change. When these conflicts are especially severe, elder abuse, both physical and psychological, may occur. Physicians need to recognize and manage abuse of the elderly. Elder abuse can be prevented by evaluating the support systems early and providing respite and counseling for stressed families. Respite care can range from attendant care in the home, to day health care, to inpatient stays to give time off to family caregivers. Information regarding elder abuse and assistance in managing cases can be obtained from the Adult Protective Services division of a local county Department of Social Services.

Financial and legal problems should be anticipated early in the disease process to maximize patient participation and avoid making important decisions during a crisis. If the question is raised early enough, the patient can assign durable power of attorney, where available. Assistance can be obtained through the support group mentioned above and from specialized legal service organizations that are available in some communities. The Adult Protective Services division of the Department of Social Services is the major resource for conservatorship problems in each county.

The management of demented elderly patients is complex and requires a great deal of skill and compassion over an extended period of time. As the number of such patients increases, primary care physicians must expand their expertise. With a multidisciplinary approach, we can begin to address the formidable burdens of the dementing illnesses in a humane way.

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Forum

The Aim of American Medicine Within the Constraints of Today's Society

Beginning in the August 1986 issue the editors of *The Western Journal of Medicine* began a forum for dialogue and discussion of the aim and purpose of medicine within the constraints now being placed on health care. Readers and others are invited to submit their views constructively and succinctly. As many as space permits will be published in future issues of the journal. At an appropriate time all the material will be collated and, if possible, the distillate will be prepared as a statement on "The Aim of American Medicine Within the Constraints of Today's Society."

MSMW

The Measure of a Society's Worth

LINDA HAWES CLEVER, MD

FRANKLY, I'M WORRIED. And tired of colloquies about "cost containment," "cost benefits" and "cost effectiveness." And also tired of the various acronyms and initials that are so pervasive in medicine these days. And I'm not at all fond of the creeping incursion of marketing terminology into our field; since *when* is health care a "product" and not a *service?*

But most of all, I'm worried.

I'm worried about analyses of health promotion which show that *prevention may increase health care costs.* Treatment of hypertension, for example, may lead to increased lifetime health costs because people live longer (albeit mainly healthier) lives. An increased life span also suggests that the Social Security System may be depleted of funds sooner and longer. What cost controls might be proposed to address this "problem?" Research in health promotion might be stifled in order to squelch the discovery of effective ways to improve health. Health promotion programs such as smoking cessation might be discouraged.

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Refer to: Clever LH: The measure of a society's worth, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Sep; 145:400

I'm also worried about the weak, the powerless, the susceptible among us: the children, the elderly, the disabled, the poor, the afflicted. What will all of the money-talk and save-money action do to them, to us? If a society's worth is measured by its care of the vulnerable, are we worthy? Or in danger of slipping badly? Or have we already slipped?

Above all, I'm worried that we will be hypnotized by the "cost-containment/effectiveness/benefits" rhetoric and the health plan debates and the marketing mystique. If we think that good health and concern for the vulnerable are important to our world, we must recognize that it may be downright *expensive* over the long haul to treat hypertension in a young person or to care for a mentally retarded person with dignity and kindness or to make sure that poor children get immunized and fed. What choice do we have?

An Issue Facing Our Society

MARSHALL B. BLOCK, MD

BEING FROM A STATE that is considered a retiree haven, this writer can appreciate but not agree with the article "Cut the Cost, Keep the Care" by George E. Pollock in the August issue.[1] He would like us to give "the best care to those in need of it regardless of their ability to pay." Perhaps in an idealized society that can be arranged, but the realities of life lead me to question whether such a goal is attainable.

Assuming we eliminate much of the waste, and get down to the nuts and bolts of medical care, the increasing age of our population and ever-increasing costs of sophisticated studies are producing a staggering health care bill for our country. Unless our society is willing to spend more than 10% to 11% of our gross national product for health care, there is no way we are going to accomplish Mr Pollock's goals. Rather, society is going to have to make some hard decisions about where to allocate its limited health care resources. We are going to have to limit care somehow, somewhere, on someone.

Unfortunately, the older we get, the sicker we are and the less productive we become. Ethically, morally and politically it is easier to limit access to services for our older population. For instance, if one had to decide who would undergo renal dialysis, would it be a 75-year-old man or a 35-year-old man with three young children? Mr Pollock and the American Association of Retired Persons I suspect recognize this fact and would have us ignore the issues I have raised.

The rationing of medical care, long an anathema to our

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society in general and to the medical profession in particular, is out in the open and needs to be discussed by all of those involved in health care. This will be the most important issue facing our society in the next decade.

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Let's Discuss a National Health Service

R. BRUCE SLOANE, MD

LOOKING AT THE CONSTRAINTS and the influx of business and government into the medical profession I wonder whether the alternative of a national health service might not be debated more than it seems to be in the circles within which I mix.

For older persons, among whom I have the distinction or unhappiness of being, and in my role as a geriatrician and director of the Pacific Geriatric Education Center at USC, I am appalled at the complexities of health insurance. To get one's benefits requires a sharp mind, assiduity and many hours a day. The present expenditures by government through federal programs, whether they be Veterans Administration, Medicare or Medicaid, are very considerable. Canada enjoys a good national health service with which my physician friends seem to be well satisfied—certainly the consumers are. The last figure I had, which may well be much out of date, was that it consumed 8.5% of the gross national product.

In Britain, where the percentage of the GNP is considerably less than this, the physicians remain well satisfied—both specialists and the ever-growing number of family practitioners and/or GPs. There is an excellent training scheme over three years for family practitioners within practicing groups of such physicians and this training is much esteemed. Most patients are satisfied and I understood, again some years ago, that the national health service covered 93% of the country and a further 7% had private insurance. These two seem to work well in a complementary fashion despite the political outcries about "paybeds" in national health service teaching hospitals. There are undoubtedly long waitlists for elective surgery and the British scheme might be regarded as the lowest common denominator. Nevertheless, it works quite well and I have never had any success in recruiting young physicians away by the lure of Los Angeles (perhaps understandable when you think about Los Angeles).

Obviously a national health service would be like this country, pluralistic and different from other national health services. However, I believe that the total wealth of the country and the rights of its citizens demand something better than what we presently have.

Programs in health care require continuity and continuum. Nowhere is this more necessary than in the care of the aging. To do this there is a need to weld a number of disciplines and services together which is very difficult in our present inchoate system. In both Canada and Britain, which I am familiar with, considerable steps have been made in coordination which did not exist prior to a national service.

On the debit side is clearly the threat of unemployment of physicians and many chasing the few desirable jobs and locations. However, with the ratio of physicians to population in California, for example, I do not believe that we are escaping that in this country and look toward the next two decades as becoming much worse in this respect. Thus there will be direction by scarcity of jobs or the demands of hospital corporations. Perhaps a national health service would be a better solution.

In addition, I believe that vital humanistic values will be restored to medicine when we are not competing so vigorously against each other.

In conclusion, and thinking at the end of what I was trying to say in the beginning, I am perhaps urging more open debate of what often seems to be a most unwelcomed topic. If this occurs I believe we will move more readily into a resolution of our present constraints.

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The Glass Is Half Full

GEORGE A. PORTER, MD

"PHYSICIAN HEAL THYSELF." Could this be the antidote for the changes facing our profession? As one reads the eight essays in the August issue reflecting on the theme "The Aims of American Medicine Within the Constraints of Today's Society," it can be viewed as a struggle for survival or a challenge to recapture lost esteem. I choose to view the glass as half full rather than half empty and suggest that the profession must establish its priorities based upon patient advocacy. Obviously, this imperative must be reconciled with the financial, social and legal restrictions that society imposes; however, alternatives do include changing society's attitude.

Common sense combined with empathy toward our patients will point us in the right direction. Putting our patients' welfare ahead of our own self-serving interests will help to recapture the lost trust and respect we have suffered during the rapid expansion of medical technology. This is not to say that we abandon progress, only that it be advanced with liberal amounts of humanism. We can no longer permit vested interests to dictate health policy anymore than we can allow the practice of corporate medicine.

We are facing major contradictions which demand acceptable compromises. How does a physician remain a patient advocate while acting as a "gatekeeper" to restrict entry to health care? We are exhorted to retain a quality service but reduce the cost of the service. When does the relief of pain and suffering become postponement of death to a medically sophisticated population with high expectations for success,

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no matter how great the risk? How can we advance medical service and yet provide a cheaper product?

For certain of these issues, a national forum convened by the leadership of medicine may be the most expeditious starting point.

Healing First, Dollars Second

MERLE S. SCHERR, MD

THE ONLY STATEMENT in the forum published in the August issue that was really interesting to me was that entitled "The Credo of An Honored Profession" by Lonnie R. Bristow.[1]

The basic theme of Dr Bristow's article is sound: "healing first, dollars second." Unfortunately not all physicians would agree with this in actual practice and belief. It is also not really "medicine against the world" although one of our biggest problems is that far too many physicians appear today to be just as guilty as the corporate world in putting dollars before healing. The house of medicine is far from unified on this subject. Were we truly and solidly behind the philosophy of "healing first, dollars second," it would be much easier to defend our honored profession and close ranks against those who would dishonor it.

It seems to me that Dr Bristow's article should be distributed both for internal consumption (within the profession) and outside consumption (by the corporate, business, governmental and regulatory segments of society). The article has substantial political value, although of course there is nothing particularly new in the philosophy presented. Some of the examples given in the article—such as corporate acquisition of medical schools and a Southern California HMO advertising that its hospitals will kick back a portion of profits to those doctors admitting patients with medical diagnoses that result in big profits to the hospital under the new Medicare system—appear to be illegal under the Medicare Quality Assurance Act of 1986 which is introduced by Senator Heinz (R-Pa) and Representative Stark (D-Calif).

We must agree with the message presented by Dr Bristow but more is required in implementing his recommendations.

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Commentary

A Focused Approach to Patients With Cancer of Unknown Primary Site

FREDERICK J. MEYERS, MD, *and* JERRY P. LEWIS, MD, *Sacramento, California*

Patients who present with apparent disseminated malignancy without an obvious primary site represent a dilemma for clinicians. Experience has shown that extensive evaluation of such patients is unrewarding. Yet, with more cancers yielding to intensive management with prolongation of life and even cures, physicians should not overlook the diagnosis of a responsive neoplasm.

Evaluating a patient with cancer with unknown primary site is best done with the expressed stated goal of diagnosing highly treatable neoplasms. This focused approach uses new techniques in the clinical laboratory to examine the pathologic material retrieved at biopsy and not by extensive radiographic interventions.

When a patient is seen with apparent extensive cancer, three questions need to be answered. First, is this really cancer? After the initial history, physical examination and routine laboratory studies, a tissue specimen should be obtained promptly. The choice of the tissue specimen to be obtained, methods by which it is obtained and the handling and fixation of the specimen are all matters of critical importance. It is, therefore, necessary to plan the biopsy and the tests done on the tissue specimen in a consultative approach between the primary physician, the surgeon, the oncologist and the pathologist.

Second, where on physical examination and routine laboratory testing are the sites of metastases? The answer to this question does not require extensive radiologic investigations, only a careful physical examination, a chemistry panel and a chest x-ray film. The first two questions logically lead to the third: What is the origin and what is the histologic type of the cancer? Occasionally a specific histologic pattern, such as squamous carcinoma or melanoma, will be found that when combined with a particular anatomic distribution identifies a clinical presentation of malignancy with still curative potential. For example, squamous carcinoma without an identifiable primary lesion presenting as a lymph node in the high cervical region and treated with resection and radical radiation therapy can result in a three-year survival of 30% and a five-year survival of 15%.[1] Melanoma without an obvious primary site can be treated with lymphadenectomy and has been reported to have a two-year survival of 40%.[2] The remainder of the patients represent one of two other problems. First is a patient with disseminated carcinoma of known histology but unknown primary—that is, adenocarcinoma of unknown primary (Table 1). Second is a patient with disseminated cancer, type unknown—that is, a poorly differentiated neoplasm (Table 2 and Table 3). A significant number of patients can be cured or can have their life substantially prolonged if a physician remembers to focus the evaluation of the patient on treatable neoplasms only. Clinicians and pathologists have available a number of techniques that can readily identify specific histologic types of cancers. Serum assays for elevated levels of hormone markers, a fresh tissue specimen for either hormone receptors or surface immunoglobulin analysis and fixed tissue on which the immunoperoxidase technique can be applied to detect the production of tissue-specific antigens are invaluable tools. The application of these diagnostic tools will allow the effective palliation or cure of many patients. These techniques represent an expansion of physicians' ability to answer question three above, "What histologic type of cancer does the biopsy show?"

A patient with disseminated cancer of known histologic pattern but unknown origin is usually a patient with adenocarcinoma of unknown primary site. Table 1 shows the five important adenocarcinomas that should be sought in a patient who presents with adenocarcinoma of unknown primary site. Prostatic carcinoma does not always present classically with an enlarged prostate and bony metastases. Adenocarcinoma in the left supraclavicular fossa can be prostatic carcinoma, and this should be specifically ruled out.[3] Although germ cell neoplasms of the testes are usually obvious, extragonadal germ cell tumors can present as adenocarcinoma of unknown primary site or, more commonly, as noted below, as large-cell undifferentiated cancer. Unsuspected thyroid cancer is best identified with the immunoperoxidase technique using an antibody directed against thyroglobulin, not with a thyroid scan.[4]

Patients with small-cell undifferentiated cancer (Table 2) will almost always have a treatable neoplasm, but the treatments are usually quite different and a specific diagnosis must be obtained.

A patient with a large-cell undifferentiated cancer frequently represents a clinical problem (Table 3). A number of investigators have described the poorly differentiated extra-

(Meyers FJ, Lewis JP: A focused approach to patients with cancer of unknown primary site. West J Med 1986 Sep; 145:403-404)

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gonadal germ cell tumor syndrome.[5] Young persons, generally men, with midline pulmonary neoplasms should have their tissue and serum assayed for human chorionic gonadotropin and α-fetoprotein. These patients respond well to germ cell tumor type therapy with a complete response rate of 35% to 50%. These tumors often resemble large-cell lymphoma because of the failure of glandular differentiation. Thus, the tissue specimen should also be examined for the presence of monoclonal immunoglobulin and submitted for electron-microscopic study that might detect a typical lymphomatous pattern.[6] Electron-microscopic examination might also be done in an effort to find elements of adenocarcinoma. Though not a neoplasm often responsive to therapy, undifferentiated carcinoma can be identified and a patient spared unnecessary therapy.

It is clear, then, that the proper evaluation of this large group of patients is best done when the primary physician caring for a patient, a surgeon and a pathologist confer before a biopsy. The biopsy specimen should be appropriately allocated for fixation, not in formalin but in a fixative that will allow immunoperoxidase analysis to be done well (such as B5 fixative)[7] and with another bit of tissue fixed for possible electron microscopy (Karnofsky's fixative). In addition, the judicious use of serum assays can also narrow the tissue-specific possibilities. Extensive radiographic examination of a patient with nuclear isotopic and computed tomographic scanning is of little value in this group of patients until a specific treatable histologic pattern is identified. Those scanning procedures perhaps become more important as a baseline to measure the effect of therapy.

A focused approach to a case of disseminated cancer is not only cost-effective but, far more important, assures that patients are given the best chance at effective palliation or cure and are spared the unnecessary toxicity of radiographic procedures or subsequent unwarranted chemotherapeutic intervention.

TABLE 1.—*Possible Laboratory Tests in Patients With an Unknown Primary Site—Patient With Adenocarcinoma*

Histologic Type Sought	*Test(s) Available*
Prostatic carcinoma	Serum acid phosphatase
	Immunoperoxidase (IP) for prostatic specific antigen
Breast carcinoma	Mammography
	Fresh tissue specimen for hormone receptors
	IP for breast antigens
Germ cell malignancy	Serum β-human chorionic gonadotropin (β-hCG) and α-fetoprotein
	IP for β-hCG and α-fetoprotein
Thyroid carcinoma	IP for thyroglobulin
Ovarian carcinoma	Ultrasound of pelvis

TABLE 2.—*Possible Laboratory Tests in Patients With Unknown Primary Site—Patients With Small-Cell Undifferentiated Cancer*

Histologic Type Sought	*Test(s) Available*
Lymphoma	Surface markers and immunoperoxidase for monoclonal immunoglobulin
Oat-cell (pulmonary or extrapulmonary)	Electron microscopy for neurosecretory granules
Ewing's sarcoma	Electron microscopy
Neuroblastoma	Electron microscopy

TABLE 3.—*Possible Laboratory Tests in Patients With Unknown Primary Site—Patients With Large-Cell Undifferentiated Cancer*

Histologic Type Sought	*Test(s) Available*
(Extragonadal) germ cell tumor	Serum β-human chorionic gonadotropin and α-fetoprotein immunoperoxidase (IP)
Large-cell lymphoma	IP for monoclonal immunoglobulin
	Electron microscopy
Carcinoma	IP for epithelial markers, such as cytokeratins
	Electron microscopy

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A Yank in London—Observations on British Medicine and Science

KENNETH I. SHINE, MD, *Los Angeles*

Recent pressures on medical expenditures in the United States have led to several comparisons with the British situation.[1,2] These have primarily focused on how health care has coped with rationing of resources, expenditure containment and the impact of the political programs of Mrs Thatcher's Tory government. For health care, Britain spends little more than half as much of its gross national product (5.6%) as America (10.8%). Governmental support of research through the Medical Research Council is actually declining in absolute as well as in relative terms.

During the 1984-1985 academic year, I had the opportunity to spend nine months on sabbatical leave in Britain, working in a London teaching hospital and conducting a research program at an associated research institute. I conducted a small practice within the National Health Service, taught a firm of house officers, participated in continuing education of groups of general practitioners who spend a week at the hospital and visited other London hospitals.

I should like to describe the ways in which I perceive British medicine and science reflect the culture of the society in which they exist. Any relevance that examination of the fiscal or structural aspects of British medical care or science has for America must be seen in the context of profound cultural differences. These are changing very little, in spite of, or because of, the efforts of current governmental leadership. I shall consider

- The expectations of the British health care consumer,
- The patient-physician relationship,
- Attitudes toward preventive medicine and health maintenance,
- Geriatrics,
- Some aspects of science,
- The current state of the National Health System as provider.

Barzini identified stoicism as that aspect of the British which uniquely characterizes them in comparison with other European peoples.[3] He contrasted this attribute to the impatience of Americans and to our conviction that we can do or fix anything. Barzini argued that these two qualities are the most alarming to Europeans when they consider their own future under the umbrella of American military and diplomatic leadership. British stoicism is seen as the "stiff-upper lip," London under the Blitz, the unquestioning queue in the post office or the supermarket, tolerance of industrial actions or acceptance of drafty construction or of the weather. The British simply do not believe that everything that does not work well should be fixed. In health care, this is seen as acceptance of the four-year wait for a total hip replacement, a nine- to ten-month wait for a bypass procedure, limited resources for dialysis or failure to offer surgical procedures to many elderly patients. A lovely 78-year-old lady for whom I cared had syncopal episodes whenever her temporary pacemaker was turned off. Although in excellent health except for her heart block, she argued fiercely that there was no need to meddle by placing a permanent pacemaker in an old woman. After three days of refusal, which was supported by her family, she agreed only on the grounds that we needed her bed for a younger patient. She did well with her pacemaker.

Even when urged to consider a surgical bypass for demonstrable disabling disease, many patients whom I saw argued strongly for alternatives. Patients and general practitioners generally shared the view that aging and illness are both in the nature of things. They did not demand help as many Americans would, but often vigorously resisted admission to hospital or procedures except under the explicit authoritative instruction of the consultant. Seen from this perspective, the limited expenditures for health, the long waits and limited services are consistent with an overall view of life that is imposed not only by economics but that reflects culture. There are, as with any generalizations of this kind, very substantial exceptions, particularly among the 5% to 6% of persons at the top of the socioeconomic system whose demand for services and expectations are high.

The Patient-Physician Relationship

Britain remains a society with a strong class structure. This is reflected in statements about the "working classes" and the "upper classes" in the speech of politicians and labor leaders. It is easily detected on the evening news by the dramatic differences in accent, tone and attitudes of members of the various classes. A situation comedy called "Mr Minister" described an upper-class politician and his friends as they tried to subvert local government plans to sell an art gallery and put the money into a football (soccer) field. The Minister

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could not allow money to move from the upper class to "those low-class types." Medicine has offered excellent opportunities for men and women from all classes and all parts of the country to enter a profession within the constraints of an educational system that is, like our own, very uneven in quality. Sampson has pointed out that the widespread elimination of the state grammar school has further polarized the educational system between state and public school sectors even more than previously.[4] But students from very diverse backgrounds qualify in medicine. In so doing, they assume an upper-class role in relation to their patients.

Many of the consulting rooms in London hospitals in which I worked were organized with a great desk and a greater distance between patient and physician. The latter spoke and the former listened. At the same time, the patients themselves had little interest in understanding their medical problems or their options. My personal patients regularly stopped me as I started to explain the pros and cons of a procedure or a therapy with the statement "I am in your hands—whatever you say." Repeatedly patients explicitly stated that they did not care to know more than that. One very intelligent and successful 35-year-old lawyer criticized me to a nurse for over 30 minutes after I asked him to keep a diary recording his symptoms and response to therapy. "He knows my coronaries, he knows the medicine, he knows the operation—why is he bothering me with this? He will have to decide about my surgery." A distinguished English High Court judge told me that he would have had the same reaction. "After all," he said, "it's a matter of trust." If something went wrong with the course of treatment, the patients with whom I dealt routinely apologized. "I'm so sorry, Doctor, I'm afraid it didn't work," one man told me while experiencing chest pain after an unsuccessful angioplasty. "I'm sorry, Doctor, but I have a bit of a fever this morning," several patients told me postoperatively.

Much is made of the lack of contingency payments to British lawyers and the different rules of law in explaining the limited amounts of malpractice litigation. My insurance premium was £264 (about $330) a year. But British patients' attitudes toward physicians and stoical acceptance of disease and its complications also contribute to this difference from the American experience. British physicians decry the invidious impact of the Amerian malpractice experience because premiums in Britain were formerly even lower. One of the most striking aspects of a patient's reaction to physicians and to illness for me was the failure of even a single English patient to complain to me about postoperative pain.

In contrast, British house officers told me that they regularly avoid caring for Americans admitted to the teaching hospitals. Americans ask too many questions, take too much time and want too much information about outcomes, I was told.

Attitudes Toward Prevention and Health Maintenance

The British view American interest in diet and exercise as "fads." They are only recently becoming aggressive in the treatment of hypertension and many British physicians emphasize the lack of convincing data about the treatment of mild hypertension. Smoking continues at a high rate—I was struck by the number of physicians who still smoke. Dental hygiene is abysmal and admitted to be so by the British, but the House of Commons still debates mandatory fluoridation.

It is remarkable that the culture that produced Snow's understanding of cholera control and in which smoking was first clearly identified as a risk factor for cancer does so little in health maintenance and prevention. Several physicians and lay people explained this relative inactivity as the result of the resistance of the British to any meddling with personal life. The government is primarily responsible for health, I was told, but even though it must run the Health Service, it was thought to be too intrusive if government were to advocate a particular diet or major changes in personal habits. In fact, at least three major government-supported studies have resulted in recommendations for programs in nutrition but none have been widely implemented. The British Heart Foundation supports extensive programs in cardiovascular research but very little in prevention. A prominent leader of the foundation told me that it relies on the media to do this education. Moreover, he asked, "what is the point of decreasing cardiovascular mortality if people will die of cancer instead?"

I believe that a principal reason for little action in these areas again arises from a fundamental willingness to accept events as they come and little conviction that major substantive changes are feasible or desirable. When I pointed out that the striking decrease in morbidity and mortality from ischemic heart disease in North America has been associated with significant prolongation of life expectancy for adults, both physicians and lay people in Britain challenged me that this was desirable. Would it not just decrease available jobs, increase chronic disability and inflate public costs for pensioners? Mortality from ischemic heart disease has shown little or no change in Britain over the past 15 years and is among the highest in Europe.[5] Yet, British physicians and the public feel no imperative to act. The London tube stations rccently contained a series of billboard signs asking for money to support cardiovascular research. These ads noted that a person had suffered a heart attack even though he is not overweight, exercises and eats muesli (cereal)—ergo, the need for research. I did not see ads in the tube about smoking cessation, hypertension control, diet or exercise.

This is not to say that other factors are not at work. Physicians and surgeons are deeply worried about cuts in the National Health Service and would much prefer to see available dollars going into increased resources for which they have responsibility. The cigarette and food lobbies are very strong in the European Economic Community, which already has a large surplus of milk and butter. On a recent television program to discuss mass prevention programs, one physician defended his position on "high-risk" identification and treatment by arguing that the medical profession should not make difficulties for the dairy farmers without incontrovertible evidence.

Americans are clearly very health conscious. Voluntary health agencies, government, the medical profession and the popular press all provide information. Americans have actively taken a role in improving their health. It is difficult to identify the aspect of health care or health maintenance that accounts for the improvement of cardiovascular morbidity and mortality in North America. But the lack of interest and effort in Britain while morbidity, mortality and life expectancy are unaffected is remarkable. While some leaders, par-

ticularly in epidemiology, continue to try, the medical profession as a whole and the government have done little.

The Special Role of Geriatrics

Britain is often cited as a leader in geriatric medicine and, indeed, it has some excellent programs. My visit, however, served to put developments in geriatrics into rather more perspective for me. First, the developments in geriatrics in Britain clearly are viewed by the government and many physicians not as a supplement or an enrichment of health care but as a substitute. Because of the British attitude toward aging, intervention and illness, many general practitioners are comfortable with watching illness develop in an older person without any assessment or intervention. They subsequently provide excellent care at home or in a geriatric facility. While this is often appropriate regardless of cultural background, I was surprised when a group of general practitioners told me that age 60 was their cutoff for assessing a patient after an acute myocardial infarction. At age 60 or older, this group insisted, a person should be treated with GTN (nitroglycerin), and no further assessment was indicated. My own experience with geriatric placement was disastrous. We kept one 84-year-old woman in hospital for four months because of the lack of a placement. Two geriatric consultants whom we consulted played a game of jurisdiction that was as accomplished as I have seen anywhere. There are distinguished geriatricians in Britain and some excellent programs that have made the most of a very difficult and limited situation. But they should be viewed in a broader context of inaction on health for the elderly, whereas we may aggressively intervene too often and too long in the care of the elderly. There ought to be some middle ground between the two approaches.

Some Aspects of Science

Britain is a wonderful place in which to carry out research while on sabbatical leave. There is an abundance of absolutely first-rate minds in a country small enough to allow one to meet many of them or at least hear them lecture. But British medical science faces some major crises. Most important, the government's science policy is miserably shortsighted. In the face of real and absolute decreases in funding, there is already concern about another "brain drain" as the best and the brightest go elsewhere. Equipment is aging rapidly, some of the best equipment is excessively expensive because of a weaker pound and some important research centers are being sharply cut or will be closed. Although there is only a minimal tax benefit from contributions, private philanthropy has contributed considerably to research support, though this cannot compensate for government reductions. While the native intelligence of British science will somehow "muddle through" these pressures, general fundamental attributes of British science and scientists warrant comment.

The elite among British students go to Oxbridge (Oxford or Cambridge). There they may prepare for careers in government, law, medicine, banking (the City), the arts, humanities and science.[4] But this is science at its most basic or unapplied sense. Engineering and technology have been identified with "trade." In traditional British class terms, the elite, the upper class, do not go "into trade." The paradox, therefore, develops that scientists at Cambridge Molecular Biology Laboratories have won seven Nobel Prizes but Britain has only a very limited presence in the biotechnology industry. British scientists pioneered in magnetic resonance imaging and computed tomographic scanning but do not have a major industrial presence in either. The government, recognizing the needs in technology, has established new schools in industry outside of Oxford, and there are recent developments toward an industrial park at Cambridge. But British scientists remain suspicious of and aloof from applications of their research. When I suggested a Cambridge Institute of Technology or an Oxford Business School as a means of legitimizing technology and management at Oxbridge, the suggestion was met with shock, disbelief and abhorrence.

British medical scientists often like to work alone and often enjoy doing everything—from the computer programming to the dishware in some cases. British medical science, like its American counterpart, will likely see increasing consolidation, with fewer centers having the critical mass of equipment and expertise to stay at the frontiers. It will be interesting to see if the attitudes of British researchers will allow this to happen.

The State of the National Health Service

My experience with the National Health Service was unexpectedly expanded when my teenaged daughter was struck by a motorcycle and seriously injured. The prehospital and emergency room care was circa 1965 in Los Angeles. In the field, there was no capability to record vital signs, start an intravenous line or communicate with a hospital. In the emergency room, more than 25 minutes elapsed before a rotating surgical house officer determined that my daughter was hypotensive. Fortunately, a consultant surgeon was called by one of my colleagues and thereafter the care was superb. The surgeons, orthopedists and nurses were well trained, alert and effective. Large quantities of blood, fresh frozen plasma and platelets were required, all of which had been obtained from volunteer donors, and the hepatitis rate is reported to be quite low. The equipment in the intensive therapy unit, however, was aging rapidly. Indeed, there was one modern volume-controlled respirator for a unit that cared primarily for respiratory patients. Though the staff took justifiable pride in their professional skills, morale was clearly down because of previous cuts and future expectancy. Physicians told me there had been a real change in a negative direction over the past six to seven years.

Nevertheless, a recent survey in the London *Times* reported that only 10% of a population sample was unhappy with the National Health Service. This is not surprising. As I have tried to indicate, the National Health Service reflects the culture and society in which it exists. So long as British expectations of life remain as they are, expectations of the National Health Service are unlikely to change. The danger is that if an already marginal system is cut more, the cost will be in additional lives without upsetting the British. A recent hospital outbreak of legionnaires' disease killed several dozen people. There was no infectious disease consultant at the hospital and, from what I read, recognition of the cause of the epidemic was slow. I find it difficult to understand why the medical profession, admittedly part of the same culture, has not more effectively communicated the meaning of unchanged rates of morbidity and mortality in ischemic heart diseases. Why are there not more papers about the death rate of patients waiting

in the queue for bypass surgery? Why is the profession so unwilling to take more aggressive steps in health care maintenance?

A member of Parliament told me that physicians are largely silent for two reasons. First, they share the same stoicism as the rest of society and believe that they will "muddle through" the cuts. Second, physicians enjoy great status that would be undermined by criticism. Many physicians added another, perhaps more important, reason. They noted that criticism would embarrass the health minister and the government. "With a stroke of his pen," one physician told me, "the minister could cut me and my colleagues down." In view of the government's response toward other challenges, this view is realistic.

Britain also suffers from a surplus of physicians. A centrally controlled system has some advantages, however. In early 1985, the minister of health announced that foreign medical graduates would be precluded from practice in Britain unless some clear national need for the physicians' services were identified. This policy was implemented overnight.

The National Health Service still maintains the separation of general practitioners from the hospital care of patients. In my experience, this has had two very deleterious effects. First, because general practitioners are cut off from regular contact with developments in diagnosis and therapy, the level of scientific competence declines over time no matter how able the physicians at graduation. Continuing education is limited. Second, general practitioners often do not know how or to whom to refer a patient who needs urgent care. My colleagues in North Wales had established a liaison so that I could be told about acutely ill patients and arrange admission rapidly. Under the circumstances, the system could be responsive. But many patients arrived in the outpatient clinic with a letter addressed to an anonymous "Dear Doctor" and with little understanding of the urgency of the patients' needs or the therapeutic options.

On balance, it was my impression that the best London teaching hospitals provide care comparable to our best county facilities. Most of the care is provided by house staff. The consultants are very able and competent but few in number. They make rounds weekly, but do not relate to most patients as private physicians in the sense that we understand. The availability of general practitioners for everyone clearly gives indigents better access to health care than exists in the United States. As I have suggested, however, there is real concern about the quality of general practice.

The growth of private medicine in Britain, which was brisk in the 1970s, has now plateaued at about 5% to 6%. The private sector is protected to some extent from catastrophic illness by transfer to the National Health Service. The *Times* of London reported that private health insurance is now a perquisite of two thirds of the top executives in industry. The falling price of oil, however, and competition from continental clinics have limited growth of health care to Middle Easterners.

Summary

As the result of my experience, I would caution Americans about examining the British system as a tool to provide future guidelines for our own. While there may be useful clues, these must be continuously evaluated in the context of the society and culture that that system creates.

British medical science has made extraordinary contributions to knowledge and health. It is now in real jeopardy from governmental cuts. While some British observers argue that they are not as wealthy as their American cousins, it is clear that the percentage of wealth spent on health, health maintenance and research remains indefensibly low and is falling. I sincerely hope that our medical colleagues in Britain take a leadership role in addressing these changes and mobilizing public opinion.

For the hospitality and generosity of my colleagues in Britain during a fascinating sabbatical leave, I am deeply grateful.

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Book Reviews

The Western Journal of Medicine does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.

DIABETES MELLITUS: Diagnosis and Treatment—Second Edition—Mayer B. Davidson, MD, Director, Diabetes Program, Cedars-Sinai Medical Center, and Professor of Medicine, UCLA School of Medicine, Los Angeles. John Wiley & Sons, Inc, One Wiley Drive, Somerset, NJ 08873, 1986. 589 pages, $25.

According to the author, the aim of this book is to "offer guidance in making those clinical decisions that are necessary only in the treatment of diabetic patients." To that end individual chapters are devoted to discussing the major issues involved in caring for patients with diabetes mellitus and include the diagnosis of diabetes, dietary treatment, insulin therapy, the use of oral hypoglycemic agents, and the diagnosis and treatment of diabetic ketoacidosis and hyperosmolar nonketotic coma. In addition to these "standard" chapters, there are also chapters on important issues that are frequently not addressed, such as the office management of a diabetic patient, the effects of emotions on diabetic control and diabetic education of nurses, patients and family. The scope of the topics discussed includes almost all clinical situations that a practitioner is likely to encounter.

This book contains a wealth of up-to-date information, much of which was published in the late 1970s and 1980s. Additionally and perhaps more important, the information presented provides practicing physicians with practical guidelines for caring for diabetic patients. Where data are available, the author discusses the scientific basis for his recommendation. Where data are not available, the author presents the rationale for his opinions. Thus this book does not represent a "cookbook" approach to the management of diabetes but rather a source of information and opinions based on the author's interpretation of the data currently available. As many of the aspects of the care of diabetic patients have not been systematically investigated, it is not surprising that not all diabetologists would agree with all of the recommendations in this book. For instance, the chapter on dietary therapy emphasizes the use of exchange lists which I have not found in my experience to be particularly useful. Nevertheless, these differences in opinion do not detract from the usefulness of this book in that it provides a unified approach to care that has been successfully used by an experienced and widely respected diabetologist. Practicing physicians can adapt the various recommendations that are applicable to their particular practice settings.

A number of very favorable features of this book should be pointed out.

- The book is easy to read and the chapters are well organized.
- The tables and figures are very carefully chosen and present important points clearly and succinctly.
- At the end of each chapter a short, carefully written synopsis of the important points of the chapter is provided.
- The book is moderately priced.

In the way of criticism the only significant suggestion that I can make for the future third edition is that in chapter 2, which discusses the general principles of treatment, the discussion of the guidelines for therapy should be expanded to include the goals of therapy, the indication and contraindications to tight control, and the risks of tight control. These topics are discussed in various areas of the book but I feel that it would be helpful to the reader to discuss these issues in one section at the beginning of the book.

In summary, this book provides a great deal of very useful, practical information. The many areas of diabetology are presented in a balanced, thoughtful manner and I can strongly recommend this book to all physicians and health professionals who are involved in the care of patients with diabetes mellitus.

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San Francisco

* * *

TROPICAL UROLOGY AND RENAL DISEASE—Edited by I. Husain, MB, FRCS, Senior Urological Consultant, Central and Mafraq Hospitals, Abu Dhabi, United Arab Emirates; former Assistant Professor of Urology, College of Medicine, King Saud University, Riyadh, Saudi Arabia. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 435 pages, $55.

Tropical Urology and Renal Disease is a pleasure to read. Dr Husain has gathered together a group of urologists, nephrologists and pathologists experienced in treating urologic and renal diseases in the tropics. This text gives practicing physicians, whether general surgeons, general practitioners or urologists who deal with tropical medicine, a concise, clinically pertinent course book.

In the first section, an excellent review of epidemiology of genital urinary disease in the tropics is precisely presented. This is then followed by a brief but complete chapter dealing with urologic examination and evaluation of a patient in the tropics. Specific tests and sophisticated radiographic evaluation may not be available in third world developing countries and this chapter addresses what can be done with limited resources.

The second section deals with renal failure in patients living in tropical areas. Differential diagnosis for the evaluation of patients with acute renal failure based on epidemiology of tropical renal diseases is concisely presented in clear easily readable format by Visith Sitprija, a nephrologist from Chulalongkron Hospital Medical School, Bangkok, Thailand. This is followed by a short review of chronic renal failure primarily aimed at maintaining renal function in patients with limited resources. Renal transplantation in the third world is briefly reviewed by Dr George Abouna from Kuwait who had developed a new transplant program there.

There are five sections each dealing with specific inflammatory or infectious etiologies. The chapter dealing with genitourinary tuberculosis is an excellent review of the subject by Drs Anwer Halim and J. G. Gow. This chapter is highlighted by the excellent line drawing examples of radiographs and color photographs of genitourinary manifestations of tuberculosis. Surgical intervention, medical treatment and prevention of this endemic problem are presented concisely and completely.

Urinary stone disease has been comprehensively treated in the section on urolithiasis. An excellent review by W. G. Robertson concerning the epidemiology of tropical urolithiasis is concisely presented. The information concerning the pathogenesis of bladder calculi in children and calcium stone disease in general populations is an excellent review, incorporating up-to-date concepts of pathophysiology. The treatment of stone disease, both surgical and medical management, is also reviewed with emphasis on techniques available in developing third world countries.

Urinary bilharziasis has extensive treatment in this text. This parasitic disease is endemic in tropical climes with significant morbidity for the affected population. Aspects of epidemiology, immunology, carcinogenesis and treatment of the varied manifestations of genitourinary bilharziasis are concisely and thoroughly reviewed.

Other areas of parasitic diseases affecting the genitourinary tract in tropical areas of the world are briefly reviewed in the following sections. Urethral stricture disease, penile carcinoma and external genitalia lesions along with urinary fistula problems are addressed in the following sections.

At the end of this text are comprehensive appendices concerning urologic instrumentation, primarily aimed at nonurologists, and a review of basic sanitation methods to improve public health as it pertains to the transmission of infectious disease in the third world.

In summary, Dr Husain has put together an excellent, concise, well thought out textbook on genitourinary manifestations of tropical diseases and primary urologic diseases as they pertain to the tropical climates in the world. This text will be of primary importance to general practitioners and general surgeons as they deal with diseases affecting the genitourinary tract in the tropical portions of the world.

EMIL A. TANAGHO, MD
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In Memoriam

Arizona Medical Association

ARMOUR, PAUL S., Phoenix. Died June 12, 1986, aged 80. Graduate of University of Louisville, 1938. Licensed in Arizona in 1944. Dr Armour was an associate member of the Arizona Medical Association.

California Medical Association

BEARG, PHILIP A., Stockton. Died May 3, 1986, aged 73. Graduate of Yale University School of Medicine, New Haven, Conn, 1937. Licensed in California in 1945. Dr Bearg was a member of the San Joaquin County Medical Society.

❦

CARPENTER, WALTER F., San Diego. Died March 20, 1986, aged 78. Graduate of University of California, Berkeley-San Francisco, 1941. Licensed in California in 1941. Dr Carpenter was a retired member of the San Diego County Medical Society.

❦

CLANCY, THOMAS PARKS, Palo Alto. Died May 2, 1986, aged 46. Graduate of Duke University School of Medicine, Durham, NC, 1965. Licensed in California in 1968. Dr Clancy was a member of the Santa Clara County Medical Society.

❦

COOPER, ALAN J., San Rafael. Died April 6, 1986, in Nicasio, aged 52. Graduate of Harvard Medical School, Boston, 1959. Licensed in California in 1969. Dr Cooper was a member of the Marin Medical Society.

❦

DUEY, HAROLD A., Oroville. Died March 23, 1986, aged 76. Graduate of the University of Nebraska College of Medicine, Omaha, 1933. Licensed in California in 1938. Dr Duey was a member of the Alameda-Contra Costa Medical Association.

❦

FOX, LEON PARRISH, San Jose. Died April 28, 1986, aged 74. Graduate of University of Louisville Medical School, 1934. Licensed in California in 1935. Dr Fox was a member and past president of the Santa Clara County Medical Society.

❦

MALONEY, PATRICK J., Merced. Died April 7, 1986, aged 62. Graduate of National University of Ireland, 1947. Licensed in California in 1951. Dr Maloney was a member and past president of the Merced-Mariposa Medical Society.

❦

PETERSON, WILLARD, Sebastopol. Died April 11, 1986, aged 65. Graduate of University of Minnesota, Minneapolis, 1943. Licensed in California in 1964. Dr Peterson was a member of the Sonoma County Medical Association.

❦

SCHERBART, JOHN DONALD, Pomona. Died March 28, 1986, in Encinitas, aged 68. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1950. MD degree from California College of Medicine, 1962. Dr Scherbart was a member of the Los Angeles County Medical Association.

❦

SCHUMACHER, GEORGE, Turlock. Died April 24, 1986, aged 73. Graduate of Loma Linda College of Medical Evangelists, 1940. Licensed in California in 1940. Dr Schumacher was a member of the Stanislaus Medical Society.

❦

SWIFT, JOHN W., Hillsborough. Died April 14, 1986, in Burlingame, aged 59. Graduate of University of California, San Francisco, 1954. Licensed in California in 1955. Dr Swift was a member of the San Mateo County Medical Society.

❦

WERDEN, DELBERT H., San Diego. Died March 7, 1986, aged 81. Graduate of Loma Linda College of Medical Evangelists, 1930. Licensed in California in 1930. Dr Werden was a member of the San Diego County Medical Society.

Montana Medical Association

ALLRED, IVAN A., Great Falls. Died March 22, 1986, aged 89. Graduate of University of Colorado, 1928. Dr Allred was a member of the Cascade County Medical Society.

❦

LAYNE, JOHN A., Great Falls. Died April 13, 1985, aged 75. Graduate of University of Minnesota, 1935. Dr Layne was a member of the Cascade County Medical Society.

New Mexico Medical Society

BICKNELL, RICHARD F., Albuquerque. Died April 17, 1986, in Albuquerque, aged 50. Graduate of Louisiana State University School of Medicine, New Orleans, 1962. Licensed in New Mexico in 1971. Dr Bicknell was a member of the Greater Albuquerque Medical Association.

❦

REPASS, PAUL E., Santa Fe. Died June 28, 1985, aged 84. Graduate of the University of Colorado School of Medicine, Denver, 1927. Licensed in New Mexico in 1973. Dr RePass was an emeritus member of the Santa Fe County Medical Society.

Utah State Medical Association

HARDING, GLEN F., Ogden. Died April 19, 1986, in Orlando, Florida, aged 76. Graduate of the University of Louisville School of Medicine, Louisville, 1936. Licensed in Utah in 1937. Dr Harding was a member of the Weber County Medical Society.

❦

SPENCER, ORSON B., St George. Died June 22, 1986, aged 68. Graduate of George Washington University, Washington, DC, 1947. Licensed in Utah in 1948. Dr Spencer was a member of the Washington County Medical Society.

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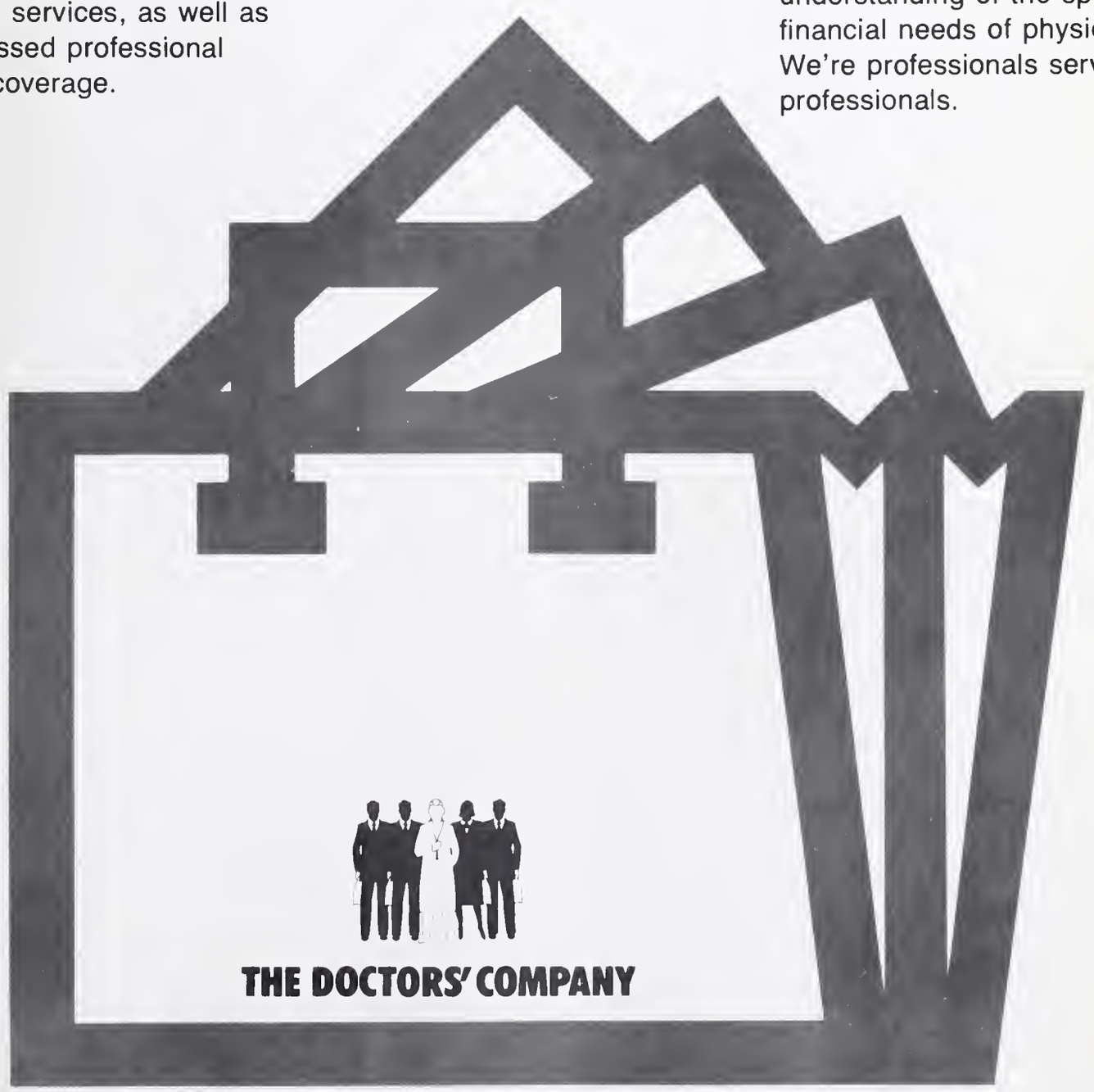

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(Continued from Page 326)

of Pediatrics Las Vegas Seminars: Pediatric Update. American Academy of Pediatrics at Caesars Palace, Las Vegas. Friday-Monday. 15.5 hrs. Fee: $295. Contact: AAP, PO Box 2134, Inglewood 90305. (213) 757-1198.

January 19-21—**Pediatrics for the Primary Care Physician.** UCSD at Vacation Village Resort, San Diego. Monday-Wednesday. 16 hrs. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 24-31—**Pediatric Emergencies.** Scripps Memorial Hospital, Encinitas at Kona Surf Resort, Hawaii. One Week. 21 hrs. Fee: $375. Contact: Edith Bookstein/AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

January 30-February 1—**25th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Marriott Hotel. Friday-Sunday. 15 hrs. Fee: $175. Contact: Wayne Herbert, MD, Children's Hospital of Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

February 5-7—**Current Concepts in Pediatric Medicine.** American Academy of Pediatrics at Holiday Inn Embarcadero, San Diego. Thursday-Saturday. 16 hrs. Fee: $330. Contact: Neal A. Baker, AAP, Division of Continuing Education, PO Box 927, Elk Grove Village, IL 60007. (800) 433-9016, or in Illinois (800) 421-0589.

PSYCHIATRY

October 24-26—**1986 Self-Psychology Conference: Clinical Advances in Self-Psychology.** UCSD at Vacation Village Resort, San Diego. Friday-Sunday. 16.5 hrs. Fee: $275. Contact: UCSD.

December 28-January 3—**Psychiatry and the Practicing Physician—"New Year '87—Maui."** Hawaii Medical Association at Royal Lahaina Resort, Kaanapali Beach, Maui. Sunday-Saturday. 16.5 hrs. Fee: $385. Contact: Joe Harrison, MD, Symposium Maui, Inc, PO Box 10185, Lahaina, HI 96761. (808) 879-8182.

RADIOLOGY

September 24-26—**Interventional Radiology Tutorial: Non-Vascular Techniques.** Sharp Memorial Hospital, San Diego at Hyatt Islandia, San Diego. Wednesday-Friday. Contact: Elizabeth Douglas, Seminar Coordinator, 7901 Frost St, San Diego 92123. (619) 541-3206.

October 6-10—**11th Annual San Diego Postgraduate Radiology Course.** UCSD at the Hotel Del Coronado, San Diego. Monday-Friday. 24 hrs. Fee: $425. Contact: R. Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

October 9-12—**11th Annual Western Regional Meeting of the Society of Nuclear Medicine.** John Ascuaga's Nugget, Sparks, Reno, Nevada. Thursday-Sunday. Contact: Society of Nuclear Medicine, Western Regional Office, PO Box 2189, Roseville 95746. (916) 791-3428.

October 10-11—**OB/GYN Ultrasound and Sonography—Update.** Sacramento Radiology Research and Education Foundation and Northern California Radiology Society. Friday-Saturday. 10 hrs. Fee: $125. Contact: John P. McGahan, MD, Sacramento Radiology Research and Education Foundation, PO Box 19184, Sacramento 95819.

October 25-29—**Radiology.** USC at Kauai, Hawaii. Saturday-Wednesday. 27 hrs. Fee: $535. Contact: USC.

October 30-November 1—**San Diego Imaging Symposium.** UCSD at US Grant Hotel, San Diego. Thursday-Saturday. 14 hrs. Contact: R. Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

November 3-7—**Diagnostic Radiology Seminars.** UCSF at Maui Marriott Hotel, Hawaii. Monday-Friday. Contact: UCSF.

December 11-13—**Advanced Ultrasound.** American College of OB/GYN at Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. 16 hrs. Contact: ACOG, 600 Maryland Ave SW, Ste 300 East, Washington, DC 20024-2588. (202) 863-2542.

January 9-12—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz Carlton Hotel, Laguna Niguel. Friday-Monday. Contact: UCSD.

January 13-16—**Chest Radiology—1987.** UCSD at Hotel Del Coronado, San Diego. Tuesday-Friday. Contact: UCSD.

January 16-18—**Annual Update on Nuclear Radiology.** UCSD at Hotel Del Coronado, San Diego. Friday-Sunday. Fee: $400. Contact: R. Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 22-24—**Practical Approach to Duplex Imaging.** UCSD at San Diego Hilton Hotel. Thursday-Saturday. Contact: UCSD.

January 30-February 1—**39th Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. 21 hrs. Fee: $350. Contact: Diane L. Johnson, Los Angeles Radiological Society, 5200 Century Blvd, Ste 920, Los Angeles 90045. (213) 642-0921.

February 2-6—**Radiology: Imaging and Intervention.** UCSD at Hotel Inter-Continental, San Diego. Monday-Friday. Contact: R. Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

February 11—**Interventional Radiology.** LLU at LLU. Wednesday. 8 hrs. Fee: $60. Contact: LLU.

February 21-28—**Radiology for Emergency and Primary Care Physicians.** Scripps Memorial Hospital, Encinitas at Royal Lahaina Resort, Maui, Hawaii. One week. 21 hrs. Fee: $375. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

SPORTS MEDICINE

November 25-28—**Sports Medicine.** American College of Sports Medicine and Children's Hospital Medical Center, Oakland at Inter-Continental Hotel, Maui. Tuesday-Friday. 25 hrs. Fee: $300. Contact: Stuart Zeman, MD, Course Chairman, 2999 Regent St, Ste 203, Berkeley 94705. (415) 540-8686.

December 10—**Orthopedic Surgery: Sports Injuries.** LLU at LLU. Wednesday. 6 hrs. Fee: $60. Contact: LLU.

SURGERY

September 27-October 4—**Temporal Bone Surgical Dissection and Cochlear Implant.** Los Angeles House Ear Institute. One Week. 62 hrs. Fee: $900. Contact: Antonio De La Cruz, MD, House Ear Institute, 256 South Lake St, Los Angeles 90057. (213) 483-4431.

September 28-October 1—**Preparing Patients for Surgery.** American College of Physicians and UCD at Monterey Hyatt Regency. Sunday-Wednesday. 14.75 hrs. Contact: ACP, Maxine Topping, (800) 523-1546, ext 207.

October 6-10—**4th Annual UCLA Symposium: A Comprehensive Review of Vascular Surgery.** Miramar-Sheraton Hotel, Santa Monica. Monday-Friday. 35 hrs. Fee: $595. Contact: UCLA.

October 11—**Lumbar Spine and Pelvis.** UCSD at the Hotel Del Coronado, San Diego. Saturday. 7 hrs. Fee: $150. Contact: R. Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

October 18-19—**1986 Regional Review Course in Hand Surgery.** American Society for Surgery of the Hand at Orthopaedic Hospital, Los Angeles. Saturday-Sunday. 12 hrs. Fee: $200. Contact: American Society for Surgery of the Hand, 3025 S Parker Rd, Ste 65, Aurora, CO 80014. (303) 755-4588.

October 18-25—**8th International Seminar on Operative Arthroscopy.** UCLA at Maui, Hawaii. One week. Contact: UCLA.

October 18-25—**Temporal Bone Surgical Dissection and Cochlear Implant.** House Ear Institute, Los Angeles. One Week. 62 hrs. Fee: $900. Contact:

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Antonio De La Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

October 24-26—**The Practical Applications of Recent Advances in Neurosurgery Research.** Scripps Clinic and Research Foundation, La Jolla. Friday-Sunday. 16.5 hrs. Fee: $250. Contact: Dept of Academic Affairs, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

November 1-8—**Temporal Bone Surgical Dissection and Cochlear Implant Courses.** House Ear Institute. One week. 62 hrs. Fee: $900. Contact: Antonio De La Cruz, MD, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

November 10-14—**Cochlear Implant.** House Ear Institute. Monday-Friday. 32 hrs. Fee: $1,350. Contact: Antonio De La Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

December 4-7—**2nd Annual Fracture Management Symposium.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Thursday-Sunday. 18 hrs. Fee: $475. Contact: UCD.

December 7-19—**Temporal Bone Surgical Dissection and Cochlear Implant.** House Ear Institute. Sunday-Friday. 100 hrs. Fee: $1,700. Contact: Antonio De La Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

January 19-21—**American Society for Surgery of the Hand's 1st Winter Meeting.** Pacific Medical Center, San Francisco. Monday-Wednesday. Contact: American Society for Surgery of the Hand, 3025 S Parker Rd, Ste 65, Aurora, CO 80014.

January 19-23—**10th Annual Postgraduate Assembly in Surgery.** UCSD at US Grant Hotel, San Diego. Monday-Friday. 30 hrs. Contact: UCSD.

OF INTEREST TO ALL PHYSICIANS

September 17-19—**Spine Update: 1986.** UCSF at San Francisco Hyatt Regency. Wednesday-Friday. Contact: UCSF.

September 18-20—**Understanding Common Adolescent Problems: A Conference on the Family.** UCSF. Thursday-Saturday. 16 hrs. Fee: $225. Contact: UCSF.

September 19-20—**Developing Services for Comprehensive AIDS Care: A Workshop.** UCSF at St Francis Hotel, San Francisco. Friday-Saturday. 11 hrs. Fee: $225. Contact: UCSF.

September 18-21—**California Conference on Applied Clinical Geriatrics.** UCD at Yountville Veterans' Home, Napa Valley. Thursday-Sunday. Contact: UCD.

September 18-21—**Making a Difference: A Workshop for International Health Volunteers.** Plastic Surgery Foundation of San Diego at San Diego Hilton Beach and Tennis Resort. Thursday-Sunday. Fee: $125. Contact: Plastic Surgery Foundation of San Diego, PO Box 33387, San Diego 92103. (619) 692-9115.

September 24-26—**Primary Care Medicine: Principles and Practice.** UCSF at Golden Gateway Holiday Inn, San Francisco. Wednesday-Friday. 19.5 hrs. Fee: $350. Contact: UCSF.

September 25-28—**Skills Update—Intensive Workshop in Sexuality.** American Association of Sex Educators, Counselors and Therapists at Sir Francis Drake Hotel, San Francisco. Thursday-Sunday. 18 hrs. Fee: $150-175. Contact: William Stull, AASECT Conference, 2333 N 3rd St, Phoenix, AZ 85004. (602) 252-2706.

September 26-27—**Samuel Merritt Hospital 41st Annual Seminar: Highlights of New Diagnostic and Therapeutic Approaches in Medicine.** Samuel Merritt Hospital, Oakland. Friday-Saturday. Fee: $50. Contact: Samuel Merritt Hospital, Medical Staff Office, Hawthorne Ave and Webster St, Oakland 94609. (415) 420-6065.

October 4-11—**Effective Diagnosis and Treatment of Infectious Diseases: California Wine Country Bicycling Tour.** University of Arizona at Guerneville. One Week. 24 hrs. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

October 15—**Alcohol and Drug Dependency.** Kaiser Permanente Medical Group at Long Beach Hyatt Hotel. Wednesday. 6 hrs. Fee: $100. Contact: Judy Harrison, Dept of Clinical Services, Southern California Permanente Medical Group, 393 E Walnut St, Pasadena 91188.

October 17-19—**Practical Gastroenterology and Flexible Sigmoidoscopy for the Practicing Physician.** UCSD and Continuing Medical Education Associates at Vacation Village Resort, San Diego. Friday-Sunday. 20 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

October 19-21—**Alcohol Related Birth Defects.** UCSD at Kona Kai Resort, San Diego. Sunday-Tuesday. 13.5 hrs. Contact: UCSD.

October 22—**Update on Diabetes.** Hospital of Good Samaritan, Los Angeles at Moseley-Salvatori Conference Center, Los Angeles. Wednesday. 7 hrs. Contact: Dolores Gay, 616 S Witmer St, Los Angeles 90017. (213) 977-2352.

October 23-25—**International Conference.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. Contact: UCSF.

(Continued on Page 416)

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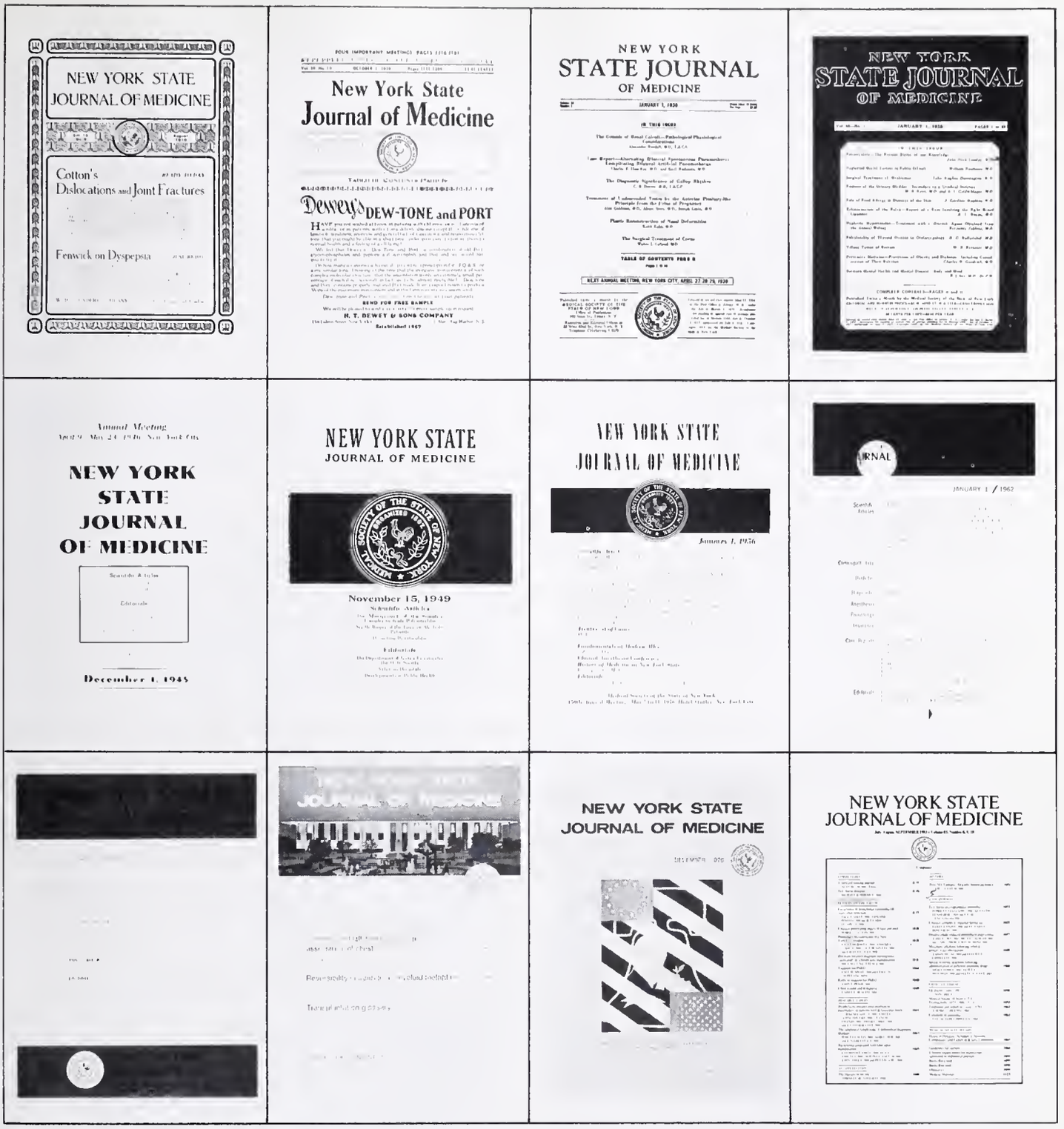

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October 23-25—**Postgraduate Institute for Monterey Counties.** CMA at Sheraton, Monterey. Thursday-Saturday. Contact: Janice Rigney, CMA.

October 31—**Managing and Controlling Asbestos Contamination/Exposure.** USC. Friday. Fee: $150. Contact: USC.

October 31-November 2—**30th Annual Western Occupational Health Conference.** Western Occupational Medical Association at Golden Gateway Holiday Inn, San Francisco. Friday-Sunday. 14 hrs. Fee: $175. Contact: Joe Donovan, WOMA, 433 Palmer Ave, Aptos 95003. (408) 688-9667.

November 3-6—**Intervention Workshop.** Scripps Memorial Hospital. Monday-Thursday. 26.5 hrs. Fee: $250. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

November 5—**Common Musculo-Skeletal Problems.** Veterans Administration Medical Center, Sepulveda. Wednesday. 5 hrs. Contact: Arun J. Mehta, MD, Rehabilitation Medicine Service (117), VAMC, Sepulveda 91343. (818) 891-2473.

November 7-8—**Medical Advances in the 80s: A Multi-Specialty Update—UCD 20th Anniversary.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. Contact: UCD.

November 8-10—**State of the Art Urology—Live Television Coverage of Surgery.** UCLA at Miramar Sheraton Hotel, Santa Monica. Saturday-Monday. 21 hrs. Fee: $400. Contact: UCLA.

November 10-14—**Intensive Care.** STAN at STAN. Monday-Friday. Contact: STAN.

November 13-15—**Progress in Impotence: Diagnosis and Therapy.** UCSD at US Grant Hotel, San Diego. Thursday-Saturday. 13 hrs. Fee: $295. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

November 14—**22nd Annual California Medical Center Staff Seminar: New Concepts in Medicine.** Los Angeles. Friday. 6 hrs. Fee: $50. Contact: California Medical Center, Kenneth L. Senter, MD, 1414 S Hope St, Los Angeles 90015. (213) 742-5750.

November 14-16—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital and Continuing Medical Education Associates at Hotel Del Coronado, San Diego. Friday-Sunday. 18 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

November 21—**Orthopedic Symposium.** Kaiser Permanente Medical Group at Marina Beach Hotel, Marina Del Rey. Friday. 7 hrs. Fee: $100. Contact: Judy Harrison, Dept of Clinical Services, Southern California Permanente Medical Group, 393 E Walnut St, Pasadena 91188. (818) 405-5000.

November 22—**Alzheimer's Disease—An Overview.** UCI at UCI. Saturday. 5.5 hrs. Contact: UCI.

November 22-29—**Stress Management: Hawaiian Islands Cruise Adventure.** University of Arizona. One Week. 24 hrs. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

November 29-December 6—**Behavioral Medicine Topics That Make Sense for Your Practice—Hawaiian Island Cruise Adventure.** University of Arizona at Hawaii. One week. 24 hrs. Contact: Epic Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

December 9—**Acquired Immune Deficiency Syndrome: Update 1986.** Daniel Freeman Memorial Hospital, Inglewood. Tuesday. 6 hrs. Contact: Daniel Freeman Memorial Hospital, (213) 674-7050, ext 3427.

December 11-12—**AIDS and the Nervous System.** UCSF at St Francis Hotel, San Francisco. Thursday-Friday. 10 hrs. Contact: UCSF.

January 12-16—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD at San Diego Hilton Hotel. Monday-Friday. 32 hrs. Fee: $325-400. Contact: UCSD.

January 16-17—**Cardiology for the Non-Cardiologist.** UCI at Long Beach. Friday-Saturday. Contact: UCI.

January 18-23—**Nevada Academy of Family Physicians Winter Assembly: Living Healthier Longer.** Caesar's Tahoe Hotel and Casino, Nevada. Sunday-Friday. 34 hrs. Fee: $400. Contact: Dottie Batchelor, NAFP, PO Box 7471, Reno, NV 89510-7471. (702) 826-5100.

January 19-21—**Pediatrics for the Primary Care Physician.** UCSD at Vacation Village Resort, San Diego. Monday-Wednesday. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 20-24—**Intensive Course in Geriatric Medicine.** UCLA at Santa Monica. Tuesday-Saturday. 33 hrs. Contact: UCLA.

January 23-25—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** Continuing Medical Education Associates at San Diego. Friday-Sunday. 20 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

January 26-28—**Recent Advances in Geriatric Medicine—1987.** UCSD at Holiday Inn Embarcadero, San Diego. Monday-Wednesday. 18 hrs. Contact: UCSD.

January 28-30—**Neurology for Non-Neurologists.** UCSD at Holiday Inn Embarcadero, San Diego.

Wednesday-Friday. 21 hrs. Fee: $375. Contact: UCSD.

January 30-February 1—**Primary Care Update—1987: A Practical Approach.** Scripps Clinic and Research Foundation at Vacation Village Resort, San Diego. Friday-Sunday. Fee: $200. Contact: Bonny Mower, Dept of Academic Affairs, PO Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

February 9-14—**UCI Family Practice Refresher Course.** UCI at Newport Beach. Monday-Saturday. Contact: UCI.

February 21-28—**Radiology for Emergency and Primary Care Physicians.** Scripps Memorial Hospital, Encinitas at Royal Lahaina Resort, Maui, Hawaii. One week. 21 hrs. Fee: $375. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

IDAHO

March 14-21—**How to Make Fitness and Health Promotion Work in Your Practice.** Sun Valley. One week. 24 hrs. Sponsors: University of Arizona, Department of Family and Community Medicine, and Epic Medical Expeditions. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley 83353. (208) 788-4995.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

September 20—**NM Physicians Mutual Liability Insurance Company Annual Loss Control Seminar.** Albuquerque. Saturday. Convention Center. Contact: K.D. Dickson, NMPMLIC, 303 San Mateo NE, Albuquerque 87108. (505) 262-1941.

September 26—**John N. Wilson, MD, Lectureship in Cardiovascular Disease.** Albuquerque. Friday.

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Marriott Hotel. 6 hrs. Cat. 1. Contact: Ann Nelson, Presbyterian Heart Institute, PO Box 26666, Albuquerque 87125. (505) 841-1438.

October 10-11—**Second Annual Balloon Fiesta Lung Disease Conference.** Albuquerque. Friday-Saturday. Contact: NM Chapter, American Thoracic Society, 216 Truman NE, Albuquerque 87108. (505) 265-0732.

October 10-12—**New Mexico Pediatric Association—Behavioral Disorders, Adolescent Adjustment Reaction, Sexual Abuse of Pre-adolescents.** Friday-Sunday. AMA Cat. 1. Contact: Charles Anderson, MD, PO Box 6132, Taos 87571. (505) 758-8651.

October 17—**Annual Cancer Symposium.** Los Alamos. Friday. Contact: Los Alamos Council on Cancer, PO Box 995, Los Alamos 87544.

November 7-8—**New Mexico Medical Society Interim Meeting—"Marketing Strategies for Private Practice" and "Gearing Up for Retirement."** Las Cruces. Friday-Saturday. Holiday Inn de Las Cruces. Contact: New Mexico Medical Society, 303 San Mateo NE, Albuquerque 87108. (505) 266-7868.

November 14-15—**Behavioral/Physiological Changes of Aging.** Albuquerque. Friday-Saturday. Marriott Hotel. Contact: Lovelace Medical Foundation, Office of Medical Education, 2425 Ridgecrest Dr SE, Albuquerque 87108. (505) 262-7000.

December 4-6—**Annual Meeting—New Mexico Chapter, American College of Physicians/New Mexico Society of Internal Medicine.** Thursday-Saturday. AMA Cat. 1. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

January 24-25—**Annual Family Practice Seminar.** Albuquerque. Saturday-Sunday. Marriott Hotel. Contact: New Mexico Chapter, American Academy of Family Physicians, PO Box 23070, Albuquerque 87192. (505) 298-5300.

February 20-22—**15th Annual Taos Lung Disease Symposium.** Taos. Friday-Sunday. Contact: NM Chapter, American Thoracic Society, 216 Truman NE, Albuquerque 87108. (505) 265-0732.

March 5-7—**New Mexico Metabolism Symposium.** Taos. Thursday-Saturday. Quail Ridge Lodge. Contact: Lovelace Medical Foundation, Office of Medical Education, 2425 Ridgecrest Dr SE, Albuquerque 87108. (505) 262-7000.

March 14—**New Mexico Pediatric Society Wylder Lecture—Pediatric Neurology.** Albuquerque. Saturday. Contact: NM Pediatric Society, (505) 758-8651.

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave, Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 W Harvard Ave, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 W Harvard Ave, Roseburg 97470. (503) 673-6641.

Emanuel Hospital, 2801 N Gantenbein St, Portland 97227:

Every Friday, 12:15 p.m. to 1:00 p.m. **Medical Grand Rounds.** Contact: Philippa McClure, Emanuel Hospital, 2801 N Gantenbein St, Portland 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Ave, Portland 97210:

Every Tuesday, 12:00 noon to 1:00 p.m. **Medicine Grand Rounds.** Neurological Sciences Buildings, First Floor Auditorium. Contact: Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Ave, Portland 97201. (503) 229-7454.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder St, Eugene 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene 97440.

(Continued on Page 420)

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

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(Continued from Page 418)

Salem Hospital, 665 Winter St SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St SE, Salem 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St SE, Salem 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St Vincent Hospital & Medical Center, 9205 SW Barnes Rd, Portland 97225. (503) 297-4411, Ext 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept of Psychiatry, Oregon Health Sciences University, Portland 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept of Medicine, Oregon Health Sciences University, Portland 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland 97201. (503) 225-7590.

EMERGENCY MEDICINE

October 23-24—**Pediatric Advanced Life Support.** Portland. Thursday-Friday. Red Lion Motor Inn/ Portland Center. Contact: OHSU-CME.

November 14-15—**Symposium on Critical Care Medicine.** Portland. Thursday-Friday. Red Lion Motor Inn/Jantzen Beach. Contact: OHSU-CME.

FAMILY PRACTICE

October 23-25—**Pacific Northwest Review of Obstetrics and Gynecology.** See below.

OBSTETRICS AND GYNECOLOGY

October 23-25— **Pacific Northwest Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion Motor Inn/Jantzen Beach. Contact: OHSU-CME.

PEDIATRICS

October 23-24—**Pediatric Advanced Life Support.** Portland. Thursday-Friday. Red Lion Motor Inn/ Portland Center. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

October 10-12—**The Salishan Conference: Cardiology.** Gleneden Beach. Friday-Sunday. Salishan Lodge. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

September 19—**American College of Physicians Regional Scientific Meeting** (Sponsor: ACP). Friday. Sheraton Hotel, Salt Lake City. Contact: C. DuWayne Schmidt, MD, 333 South 900 East, Salt Lake City 84102. (801) 535-8149.

September 19-20—**Postgraduate Laser Program—GYN** (Sponsor: UUMC). Friday-Saturday. University of Utah Medical Center, Salt Lake City. 10 hrs. Contact: John Dixon, MD, (801) 581-2256.

September 25-26—**Postgraduate Laser Program—Urology** (Sponsor: UUMC). Thursday-Friday. University of Utah Medical Center, Salt Lake City. 10 hrs. Contact: John Dixon, MD, (801) 581-2256.

October 6-8—**Occupational Low Back Pain** (Sponsor: UUMC). Monday-Wednesday. Snowbird Resort. 15 hrs. Contact: Connie Crandall, (801) 581-3841.

October 31-November 1—**Stress, Emotion and Heart Disease** (Sponsor: UUMC). Friday-Saturday. Marriott Hotel, Salt Lake City. 15 hrs. Contact: Hilmon Castle, MD, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143, (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
UVH:	Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

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University of Cape Town
Professor Emeritus,
University of Cape Town
Scientist in Residence
Baptist Medical Center
Oklahoma City, Oklahoma

Fred Crawford, MD
Professor and Chairman,
Department of
Cardio-Thoracic Surgery
Medical University of South Carolina
Charleston, South Carolina

Mark M. Levinson, MD
Assistant Professor,
Cardiothoracic Surgery
Director, Artificial Heart Program
University of Arizona Health Sciences Center
Tucson, Arizona

William W. O'Neill, MD
Assistant Professor,
Internal Medicine
Director of Cardiac Catherization Laboratory
University of Michigan
Ann Arbor, Michigan

For further information contact Jan Hodge-VonDeBur at (303) 475-5675 or write: Continuing Medical Education, 1400 E. Boulder St., P.O. Box 1326-80901, Colorado Springs, CO 80901.

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November 7-8—**Advanced Trauma Life Support** (Sponsor: UUMC). Friday-Saturday. Quality Inn, Salt Lake City. 16 hrs. Contact: Carla Holmes, (801) 533-6608.

November 20-21—**Postgraduate Laser Program—GI.** (Sponsor: UUMC). Thursday-Friday. University of Utah Medical Center, Salt Lake City. 10 hrs. Contact: John Dixon, MD, (801) 581-2256.

January 5-14—**Hip and Knee Bioskills Workshop** (Sponsor: UUMC). 10 days. Snowbird Resort. 15 hrs. Contact: Aaron Hoffman, MD, (801) 581-8664.

January 20-22—**Pulmonary Function Testing** (Sponsor: UUMC). Tuesday-Thursday. RMCOEH, University of Utah Medical Center. 18 hrs. Contact: Connie Crandall, (801) 581-8719.

February 1-6—**Diagnostic Imaging/Interventional Radiology** (Sponsor: UUMC). Sunday-Friday. Snowbird Resort. 20 hrs. Contact: Judy Gallegos, (801) 581-8188.

February 10-13—**Family Practice Refresher Course** (Sponsor: UUMC). Tuesday-Friday. Westin Hotel Utah, Salt Lake City. 28 hrs. Contact: Denise Denton, (801) 581-5224.

February 11-14—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wednesday-Saturday. Salt Lake City. 17 hrs. Contact: (801) 521-1221.

February 12-14—**Rigid Fixation Techniques/Craniomaxillofacial Surgery** (Sponsor: UUMC). Thursday-Saturday. Snowbird Resort. 20 hrs. Contact: Louis Morales, MD, (801) 581-8664.

February 14-21—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). One week. Park City Resort. 25 hrs. Contact: John Matsen, MD, (801) 581-7480.

February 16-20—**Surgical Pathology Workshops** (Sponsor: UUMC). Monday-Friday. Park City Resort. 20 hrs. Contact: Tom Colby, MD, (801) 581-7480.

February 19-21—**Mid-Winter Trauma Seminar for Military and Civilians** (Sponsor: UUMC). Thursday-Saturday. Westin Hotel Utah, Salt Lake City. 15 hrs. Contact: Clayton Petty, MD, (801) 581-6393.

February 20-24—**Postgraduate Course in Anesthesiology** (Sponsor: UUMC). Friday-Tuesday. Salt Lake City. 16 hrs. Contact: Theodore Stanley, MD, (801) 581-6393.

February 21-25—**Annual Ob-Gyn Update** (Sponsor: UUMC). Saturday-Wednesday. Park City. 15 hrs. Contact: James Scott, MD, (801) 581-5501.

February 22-27—**Park City Dermatology Seminar** (Sponsor: UUMC). Sunday-Friday. Park City. 18 hrs. Contact: Gerald Kruegar, MD, (801) 581-7837.

February 25-28—**Gynecologic Oncology** (Sponsor: UUMC). Wednesday-Saturday. Park City. 15 hrs. Contact: James Scott, MD, (801) 581-5501.

February 26-28—**Arthroscopic Surgery** (Sponsor: UUMC). Thursday-Saturday. Westin Hotel Utah, Salt Lake City. 21 hrs. Contact: Robert Metcalf, MD, (801) 581-7601.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

September 18-19—**Brain Injury.** Seattle. Thursday-Friday. Contact: U/W.

September 18-21—**Washington State Medical Association** Annual Meeting. Spokane. Thursday-Sunday. Inn at the Park. Contact: WSMA.

September 25-27—**American Society of Internal Medicine Annual Meeting: Reimbursement, Re-**

(Continued on Page 424)

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 623-4801.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

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(Continued from Page 422)

view & Retooling: On the Road Again. Seattle. Thursday-Saturday. Contact: ASIM, (202) 289-1700.

September 27—**Arthur A Ward Symposium.** Seattle. Saturday. U/W Health Sciences Building. Contact: U/W.

October 3—**Topics in Pulmonary Medicine: Pulmonary Infection.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

October 15—**Legal Aspects of Occupational Health.** Seattle. Wednesday. Center for Occupational Health and Safety. Contact: U/W.

October 17-18—**Alternative Delivery Systems: Strategies for Physician Control.** Washington, D.C. Friday-Saturday. Contact: American Society of Internal Medicine, (202) 289-1700.

October 24—**Twentieth Annual Cancer Conference: Lung Cancer.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

October 29-30—**Focus: Critical Care.** Tacoma. Wednesday-Thursday. Contact: College of Medical Education-Tacoma.

November 6-7—**Current Concepts in Drug Therapy.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

November 7—**Symposium on the Diabetic Foot.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

November 12-14—**Ventilation: Principles and Applications.** Seattle. Wednesday-Friday. NW Center for Occupational Health and Safety. Contact: U/W.

November 13-14—**Molecular Medicine.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

November 13-14—**Emergency Physicians.** Thursday-Friday. Location to be announced. Contact: American College of Emergency Physicians, Washington Chapter, (206) 441-9762.

November 21-22—**Short-Term Therapy.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

December 4-5—**Worker Health and Safety at Hazardous Waste Site.** Seattle. Thursday-Friday. NW Center for Occupational Health and Safety. Contact: U/W.

December 5—**Practical Pediatrics.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

December 5-6—**Northwest Urologists/Washington State Urology—1986 Annual Meeting.** Tacoma. Friday-Saturday. Tacoma Sheraton. Contact: WSMA.

January 15-16—**Agricultural Health and Safety.** Seattle. Thursday-Friday. NW Center for Occupational Health and Safety. Contact: U/W.

January 23—**Topics in Pulmonary Medicine: Interstitial Lung Disease.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

February 4-6—**Spirometry Training for Worker Screening.** Seattle. Wednesday-Friday. NW Center for Occupational Health and Safety. Contact: U/W.

February 6-7—**Modern Concepts in Allergy.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 20-21—**Office Gynecology for the Primary Care Physician.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 26-27—**Health and Safety of Firefighters.** Seattle. Thursday-Friday. NW Center for Occupational Health and Safety. Contact: U/W.

March 13—**Recent Developments in Occupational Medicine.** Seattle. Friday. NW Center for Occupational Health and Safety. Contact: U/W.

March 20—**Neuro-Opthalmology Seminar.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

WYOMING

February 28-March 7, 1987—**Selected Topics in Wilderness and Environmental Medicine.** A nordic skiing adventure at Yellowstone National Park. One week. Sponsors: University of Arizona, Department of Family and Community Medicine, and Epic Medical Expeditions. 24 hrs. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995. ◆

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ORTHOPAEDICS—Private practice opportunity in Espanola, New Mexico. Financial assistance with income guarantee. Easy access to all forms of recreation—just 20 miles north of Santa Fe. For further information, please submit CV to: Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or, call 1-800-545-4030, Ext. 8300.

PACIFIC NORTHWEST: Beautiful Coeur d'Alene, Idaho, the capital of the Inland Northwest's extensive network of pristine lakes, is in immediate need of a staff physician to join Group Health Northwest, a family practice staff model HMO, now expanding into North Idaho. Excellent benefit package, association with the 24 physicians of Group Health of Spokane, adequate call sharing, vacation and CME coverage, but with the independence of a small practice in a beautiful lakeside town which has a hospital and most specialties represented. Board certified FP's with OB experience desired. Contact Thomas Kearney, Group Health of North Idaho, PO Box 5339, Coeur d'Alene, ID 83814.

CARDIOLOGIST, INVASIVE—150-physician, multispecialty, prepaid group located in the San Francisco Bay Area wishes to add another Cardiologist/Internist. Practice includes large volume of referrals for invasive procedures. Doppler-echo skills required. University affiliation available. Please contact: E. Andrews Neal, MD, The Permanente Medical Group, Inc., 260 International Circle, San Jose, CA 95119; Telephone (408) 972-6340.

SEATTLE—Internist or Family Practitioner, Board certified, to join primary care partnership group committed to stable physician-patient relationships, assured quality of care, professional management and marketing, in cooperation with Saint Cabrini Hospital of Seattle. Contact R. Morrison, MD, 901 Boren, #1530, Seattle, WA 98104; (206) 682-5071.

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OB/GYN: Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, Administration, 1400 East Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

GYNECOLOGIST—Needed in Ketchum/Sun Valley multispecialty clinic. Excellent climate, unlimited recreation facilities and very good schools. Income dependent on productivity. Dr Bryan Stone, PO Box 2198, Ketchum, ID 83340; (208) 726-9361.

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NORTHERN CALIFORNIA, Emergency Medicine—Full-time positions available in the Emergency Room at The University of California, Davis, Medical Center. The University serves a large region of Northern California and is a major trauma center. Emergency physicians teach and supervise medical students and housestaff in addition to treating patients, primarily. Opportunities exist for involvement in other School of Medicine teaching activities. Applicants should send curriculum vitae to Robert W. Derlet, MD, University of California Davis Medical Center, 2315 Stockton Blvd, Department of Emergency Medicine, Trailer 1219, Sacramento, CA 95817.

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MD NEEDS—SOUTHERN CALIFORNIA ONLY—FPs, GP, IM, OB/GYN, OR and other subspecialities needed for private groups and associations. Baker, Ellerd and Associates, Inc., 16200 Ventura Blvd., Ste. 426, Encino, CA 91436; call (818) 995-4311.

EMERGENCY MEDICINE Career opportunities for primary care physicians are immediately available with Spectrum throughout Arizona. Openings are for emergency department medical directors and full-time staff physicians at select client hospitals in Arizona. You can choose the location and practice situation that meets your needs. Guaranteed competitive rate of compensation, full protection of occurrence malpractice insurance coverage, plus Medical Directors receive paid life, health, disability and dental insurance which includes dependents. For more details on these excellent opportunities in Arizona, contact Bill Salmo, Spectrum Emergency Care, 6275 Lehman Dr., Ste. C202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

RURAL COLORADO, OB/GYN: BC/BE OB/GYN to join three FPs, three Internists, and General Surgeon with growing group. Guaranteed salary and fringes plus incentives. Excellent opportunity for person interested in rural living, mountain recreation, health care delivery for underserved populations. Full- or part-time position. Send CV to Michael Bloom, 204 Carson Ave., Alamosa, CO 81101; (303) 589-5161.

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(Continued on Page 428)

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(Continued from Page 426)

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SANTA BARBARA COUNTY seeks licensed California physician with American Specialty Board certification for Staff Physician Specialist. Position in Communicable Disease Control, Public Health. $76,728/year (approximately). Prefer public health experience. Contact Santa Barbara County Personnel, 1226 Anacapa St., Santa Barbara, CA 93101; (805) 963-7155. AA/EOE.

FAMILY PRACTICE—Multispecialty family care oriented group needs additional Family Practice Physicians. Excellent practice opportunity in a dynamic Southwest city; good benefits and salary plan. Send CV to: D. R. Molesworth, Administrator, The Tucson Clinic, P.C., PO Box 26926, Tucson, AZ 85726.

INTERNAL MEDICINE—Multispecialty group needs additional Internists. A growing group in a dynamic Southwest community; excellent practice; benefits; and investment opportunities. Send CV to: D. R. Molesworth, Administrator, The Tucson Clinic, P.C., PO Box 26926, Tucson, AZ 85726.

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PEDIATRICIAN—Seeking pediatrician to serve the communities of Central Pinal County. Casa Grande Regional Medical Center is a 100 bed, 1984 constructed general and acute care hospital. Please send CV to: Administrator, Casa Grande Regional Medical Center, 1800 E. Florence Blvd., Casa Grande, AZ 85222.

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SURGEON—General Surgeon needed to serve Casa Grande Regional Medical Center, a 100 bed, general and acute care hospital opened in 1984. Please send CV to: Administrator, Casa Grande Regional Medical Center, 1800 E. Florence Blvd., Casa Grande, AZ 85222.

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: 1987: Date and place to be announced.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 863-5522. Annual Meeting: March 6-11, 1987, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 18-20, 1986, Snowmass.

Hawaii Medical Association—320 Ward Ave, Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1986, Westin Ilikai Hotel, Honolulu.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1987: Date and place to be announced.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 2-4, 1986, Holiday Inn, Bozeman.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 30-May 3, 1987, Ormsby House, Carson City.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 6-8, 1987, Clarion Four Seasons, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): 1987: Date and place to be announced.

Utah State Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 10-12, 1986, Yarrow Holiday Inn, Park City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 623-4801. Annual Meeting: September 18-21, 1986, Spokane.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1987: Date and place to be announced.

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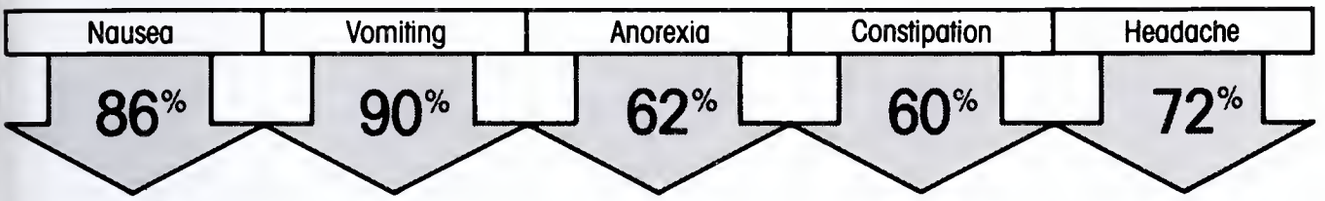

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References: 1. Data on file, Hoffmonn-Lo Roche Inc., Nufley, NJ. 2. Feighner JP, *et ol: Psychopharmocology 61*:217-225, Mor 22, 1979.

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Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

***Usage in Pregnancy*: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady state concentrations of the tricyclic drugs. Concomitant use of Limbitrol with other psychotropic drugs has not been evaluated, sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impatence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:

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Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

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Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol DS (double strength) Tablets, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol Tablets, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: *Double strength (DS) Tablets*, white, film-coated, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt), and *Tablets*, blue, film-coated, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt). Available in bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.

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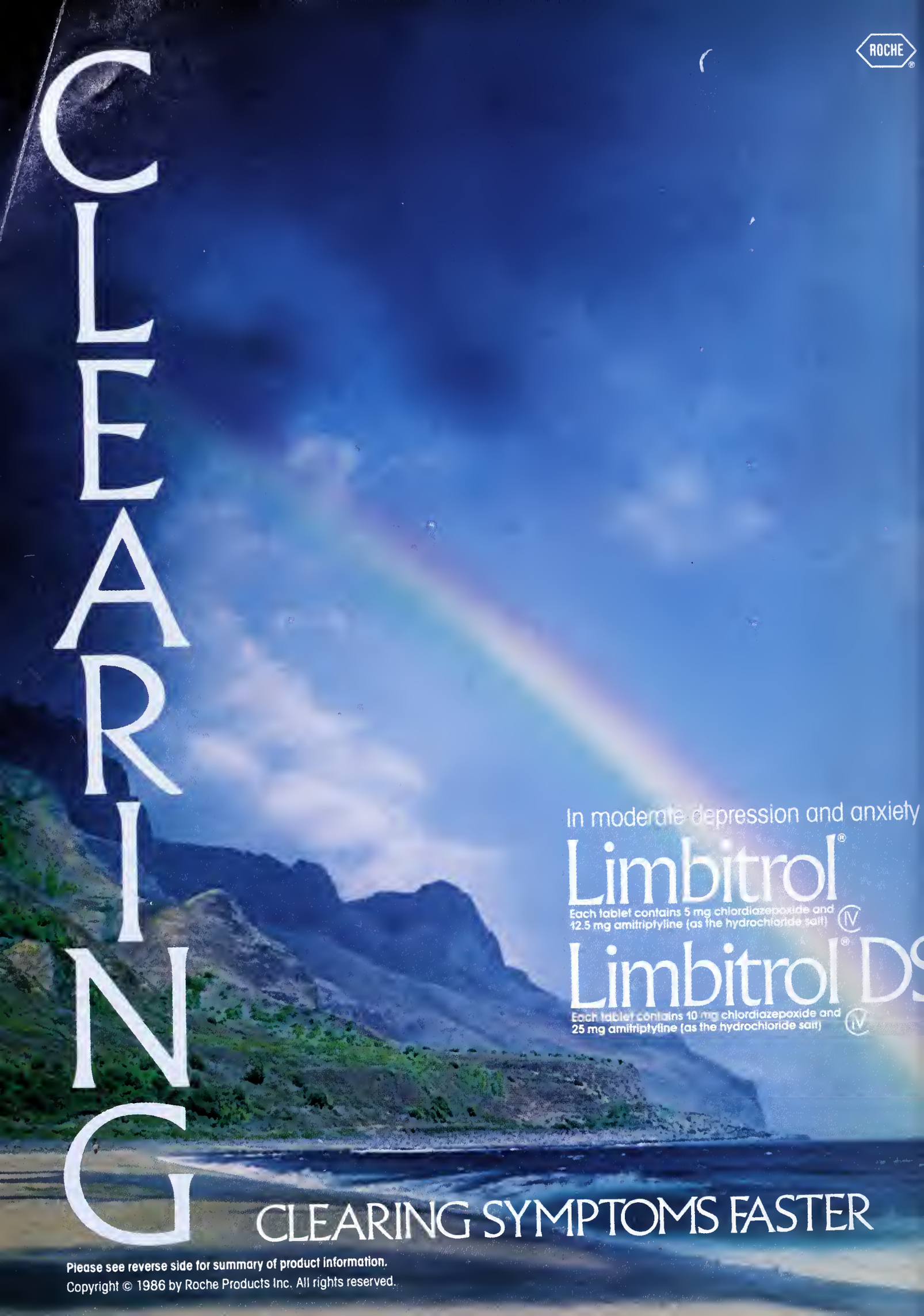

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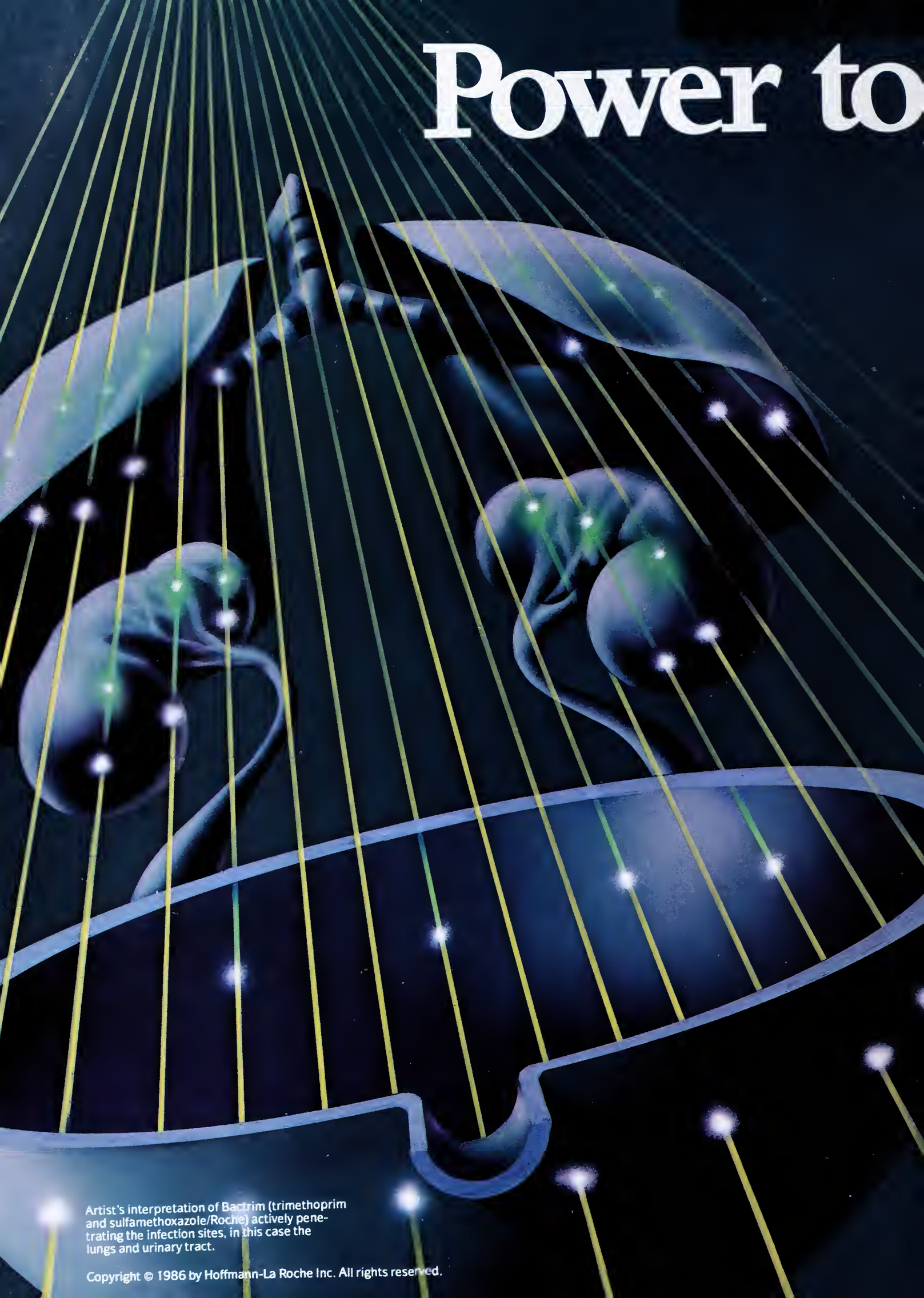

Artist's interpretation of Bactrim (trimethoprim and sulfamethoxazole/Roche) actively penetrating the infection sites, in this case the lungs and urinary tract.

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overpower

the power of penetration into infected tissues and fluids
The strong penetrating power of Bactrim into tissues and fluids is a real benefit in the treatment of acute exacerbations of chronic bronchitis, recurrent urinary tract infections and acute otitis media when caused by susceptible strains of pathogens.

the power of concentration through high levels at the site of infection...
In infections like these, Bactrim concentrates its full antibacterial powers at the site of infection, such as the bronchioles or urinary tract.

and effective levels at the source of reinfection
Bactrim also penetrates into nearby tissues and fluids, often inhibiting the growth of bacterial colonies that might serve as the foci of future infections.[1,2]

the power of spectrum through broad-range activity
Bactrim has proven effective *in vitro* against a broad range of pathogens, including *E. coli, Klebsiella pneumoniae, Enterobacter* and *Proteus* (as in recurrent urinary tract infections); *S. pneumoniae* and *H. influenzae* (as in acute exacerbations of chronic bronchitis and acute otitis media). After years of use, little change in bacterial resistance has been seen.[3] And Bactrim has even been reported effective against various ampicillin-resistant strains *in vitro*.[4] However, *in vitro* data do not necessarily correlate with clinical results.

B.I.D. convenience and economy
Some additional benefits: The convenience of *b.i.d.* dosage and economy are designed to encourage patient compliance.

Adequate fluid intake should be maintained during therapy. Bactrim is contraindicated in infants less than two months, in pregnancy at term, during lactation and in patients with documented megaloblastic anemia due to folate deficiency.

Specify Bactrim DS
To be certain your patients get the brand and results you want for them, specify Bactrim DS and "No Generic Substitution," following your state regulations.

References: 1. Rubin RH, Swartz MN: *N Engl J Med 303*:426-432, Aug 21, 1980. 2. Stamey TA, Condy M: *J Infect Dis 131*:261-266, Mar 1975. 3. BAC-DATA Medical Information Systems, Inc., Volume II, 1985. 4. Data on file, Hoffmann-La Roche Inc., Nutley, NJ.

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Before prescribing, please consult complete product information, a summary of which follows:
CONTRAINDICATIONS: Hypersensitivity to trimethoprim or sulfonamides; documented megaloblastic anemia due to folate deficiency, pregnancy at term and during the nursing period, infants less than two months of age.
WARNINGS: FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS.
BACTRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. Clinical signs, such as rash, sore throat, fever, pallor, purpura or jaundice, may be early indications of serious reactions. In rare instances a skin rash may be followed by more severe reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis or serious blood disorder. Perform complete blood counts frequently.
BACTRIM SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A ß-hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Bactrim than with penicillin.
PRECAUTIONS: *General:* Give with caution to patients with impaired renal or hepatic function, possible folate deficiency (e.g., elderly, chronic alcoholics, patients on anticonvulsants, with malabsorption syndrome, or in malnutrition states) and severe allergies or bronchial asthma. In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur, frequently dose-related.
Use in the Elderly: May be increased risk of severe adverse reactions in elderly, particularly with complicating conditions, e.g., impaired kidney and/or liver function, concomitant use of other drugs. Severe skin reactions, generalized bone marrow suppression (see WARNINGS and ADVERSE REACTIONS) or a specific decrease in platelets (with or without purpura) are most frequently reported severe adverse reactions in elderly. In those concurrently receiving certain diuretics, primarily thiazides, increased incidence of thrombocytopenia with purpura reported. Make appropriate dosage adjustments for patients with impaired kidney function (see DOSAGE AND ADMINISTRATION).
Use in the Treatment of Pneumocystis Carinii *Pneumonitis in Patients with Acquired Immunodeficiency Syndrome (AIDS):* Because of unique immune dysfunction, AIDS patients may not tolerate or respond to Bactrim in same manner as non-AIDS patients. Incidence of side effects, particularly rash, fever, leukopenia, with Bactrim in AIDS patients treated for *Pneumocystis carinii* pneumonitis reported to be greatly increased compared with incidence normally associated with Bactrim in non-AIDS patients.
Information for Patients: Instruct patients to maintain adequate fluid intake to prevent crystalluria and stone formation.
Laboratory Tests: Perform complete blood counts frequently; if a significant reduction in the count of any formed blood element is noted, discontinue Bactrim. Perform urinalyses with careful microscopic examination and renal function tests during therapy, particularly for patients with impaired renal function.
Drug Interactions: In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Bactrim may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. Keep this in mind when Bactrim is given to patients already on anticoagulant therapy and reassess coagulation time. Bactrim may inhibit the hepatic metabolism of phenytoin. Given at a common clinical dosage, it increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When giving these drugs concurrently, be alert for possible excessive phenytoin effect. Sulfonamides can displace methotrexate from plasma protein binding sites, thus increasing free methotrexate concentrations.
Drug/Laboratory Test Interactions: Bactrim, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs if methotrexate is measured by a radioimmunoassay (RIA). The presence of trimethoprim and sulfamethoxazole may also interfere with the Jaffe alkaline picrate reaction assay for creatinine, resulting in overestimations of about 10% in the range of normal values.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: Long-term studies in animals to evaluate carcinogenic potential not conducted with Bactrim. *Mutagenesis:* Bacterial mutagenic studies not performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim demonstrated to be nonmutagenic in the Ames assay. No chromosomal damage observed in human leukocytes *in vitro* with sulfamethoxazole and trimethoprim alone or in combination; concentrations used exceeded blood levels of these compounds following therapy with Bactrim. Observations of leukocytes obtained from patients treated with Bactrim revealed no chromosomal abnormalities. *Impairment of Fertility:* No adverse effects on fertility or general reproductive performance observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole.
Pregnancy: Teratogenic Effects: Pregnancy Category C. Trimethoprim and sulfamethoxazole may interfere with folic acid metabolism; use during pregnancy only if potential benefit justifies potential risk to fetus. Nonteratogenic Effects: See CONTRAINDICATIONS section.
Nursing Mothers: See CONTRAINDICATIONS section.
Pediatric Use: Not recommended for infants under two months (see INDICATIONS and CONTRAINDICATIONS sections).
ADVERSE REACTIONS: Most common are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria). **FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS (SEE WARNINGS SECTION)** *Hematologic:* Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia. *Allergic Reactions:* Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schoenlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash. Periarteritis nodosa and systemic lupus erythematosus have been reported. *Gastrointestinal:* Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia. *Genitourinary:* Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria. *Neurologic:* Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache. *Psychiatric:* Hallucinations, depression, apathy, nervousness. *Endocrine:* Sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents; cross-sensitivity may exist. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. *Musculoskeletal:* Arthralgia, myalgia. *Miscellaneous:* Weakness, fatigue, insomnia.
DOSAGE AND ADMINISTRATION: Not recommended for use in infants less than two months of age.
URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN: *Usual adult dosage* for urinary tract infections is one DS tablet, two tablets or four teaspoonfuls (20 ml) *b.i.d.* for 10 to 14 days. Use identical daily dosage for 5 days for shigellosis. *Recommended dosage for children* with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses every 12 hours for 10 days. Use identical daily dosage for 5 days for shigellosis. *Renal Impaired:* Creatinine clearance above 30 ml/min, give usual dosage; 15-30 ml/min, give one-half the usual regimen; below 15 ml/min, use not recommended.
ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS: Usual adult dosage is one DS tablet, two tablets or four teasp. (20 ml) *b.i.d.* for 14 days.
PNEUMOCYSTIS CARINII PNEUMONITIS: Recommended dosage is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.
HOW SUPPLIED: *DS (double strength) Tablets* (160 mg trimethoprim and 800 mg sulfamethoxazole)—bottles of 100, 250 and 500; Tel-E-Dose™ packages of 100; Prescription Paks of 20. *Tablets* (80 mg trimethoprim and 400 mg sulfamethoxazole)—bottles of 100 and 500; Tel-E-Dose™ packages of 100; Prescription Paks of 40. *Pediatric Suspension* (40 mg trimethoprim and 200 mg sulfamethoxazole per teasp.)—bottles of 100 ml and 16 oz (1 pint). *Suspension* (40 mg trimethoprim and 200 mg sulfamethoxazole per teasp.)—bottles of 16 oz (1 pint).
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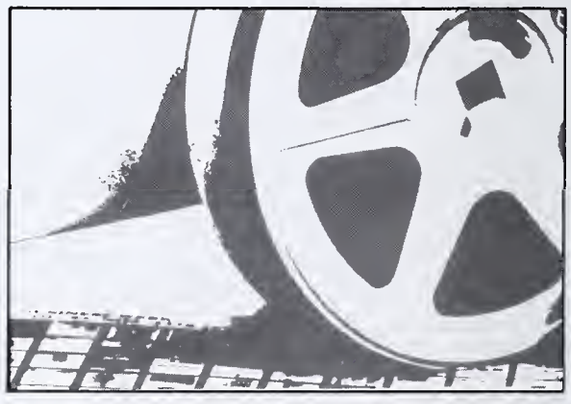

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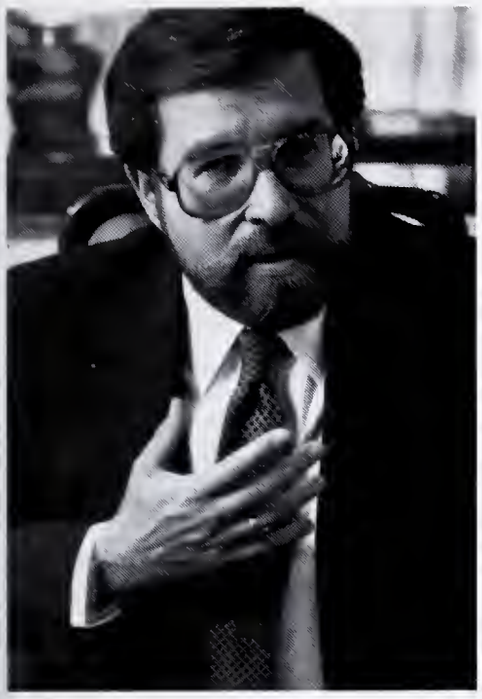
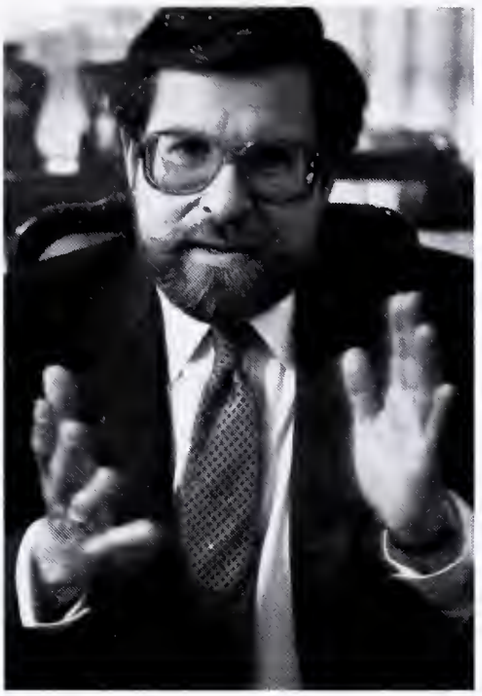


"A lot of people think Blue Cross has the opportunity to be the most successful insurance carrier in the Western United States. I happen to be one of them. In fact, that's the main reason I came out here. To be a part of that. There are excellent people in this organization. But what I found was that the organization was so large it was tying their hands. That's why our first move was to reorganize into smaller units. More manageable units. With a much clearer focus as to results."



"Already, we've been talking to a lot of physicians and hospitals face-to-face, getting their input on how we can become a more service-oriented organization. Their biggest concern is that our claim payments are on the slow side. And they're right. But I can honestly say improvements with that are already in the works. As far as individual and group plans go, they seem to like what we're doing. They understand that as hard as it is today to keep costs down, no one is doing a better job."

"We're in this together. We can't function without the hospitals and physicians, and vice-versa, they can't operate without us. And it's true, times are tough right now. But recently I was elected to the Board of Directors of the Southern California Hospital Association. So there's an exchange going on of thoughts and ideas. And that's encouraging. It can only make things better. After all, our goal is to make it as easy as possible for hospitals. To always be there when they need us. And I think we're heading in the right direction."

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In mild-to-moderate hypertension†

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- **8 years in clinical use**
  CAPOTEN has an established record of practical clinical usage, spanning nearly a decade.

- **16 million prescriptions**
  Since its successful introduction in the U.S., CAPOTEN has earned the prescribing confidence of physicians.[1]

- **5 million patients**
  CAPOTEN has provided well-tolerated therapy for over 5 million patients worldwide.

†CAPOTEN may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. See INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

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More than 3,000 informative articles have been published about CAPOTEN.

Convenient, well-tolerated therapy that promotes patient compliance

Comparison of Adverse Effects for CAPOTEN (≤ 100 mg) versus Placebo in Hypertensive Patients with Normal Renal Function (N = 1,622)‡[2]

ADVERSE EFFECT	CAPOTEN (N = 1,174) (% affected)	Placebo (N = 448) (% affected)
Headache	5.2	6.9
Rash	3.7	2.5
Dizziness	3.5	2.0
Nausea	3.2	2.0
Fatigue	3.1	2.0
Taste alteration	1.5	1.1
Gastrointestinal	1.4	0.7
Diarrhea	1.1	1.1

‡None of the differences between captopril and placebo was statistically significant. For the most part, adverse effects were mild and transient and usually did not require discontinuation of therapy. Only 5.5% of the patients in this data base discontinued because of an adverse effect. Data include adverse effects for CAPOTEN with an incidence greater than 1%.

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INDICATIONS: Hypertension – CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia (<1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine <1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. Of reported cases, about half had serum creatinine ≥1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria – Total urinary proteins >1 g/day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy, patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension – Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function,* Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction.

Surgery/Anesthesia – If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C – There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic – Neutropenia/agranulocytosis have occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients – reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur, see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia – About 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg also available in bottles of 1000), and in UNIMATIC® single dose packs of 100 tablets. (J3-658D)

References:

1. PDS Alpha, *National Prescription Report,* Pharmaceutical Data Services, Subsidiary of McKesson Corporation.
2. Data on file, Squibb Institute for Medical Research

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INNOVATORS IN CARDIOVASCULAR MEDICINE

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From the Family Practice Residency of Idaho, Boise, affiliated with the Department of Family Medicine, University of Washington School of Medicine, Seattle.

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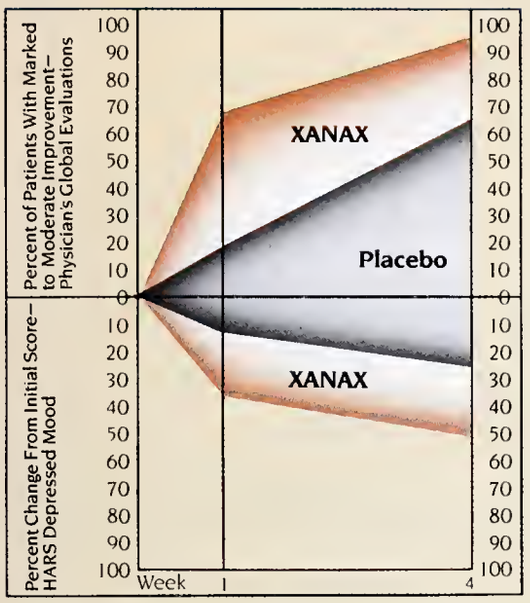
In 7 of 10
anxious
geriatrics...
Anxiety and
depressive
symptoms
go hand
in hand.

Xanax effectively relieves anxiety with associated depressive symptoms.



In a recent clinical study[1] of 83 geriatric patients with clinical anxiety, 73% were diagnosed as having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than does placebo in reducing the Hamilton Anxiety Rating Scale Total Score and individual items, including depressed mood (see Figure).

With clinical advantages for geriatric patients.

- Effectively relieves the symptoms of anxiety
- Also relieves anxiety with associated depressed mood
- Well tolerated—side effects, if they occur, are generally observed at the beginning of therapy and usually disappear with continued medication. Drowsiness and light-headedness were the most commonly reported adverse reactions
- Does not cause cardiovascular toxicity
- **Specific geriatric dosage**—0.25 mg, two or three times daily

1. Cohn JB: Double-blind safety and efficacy comparison of alprazolam and placebo in the treatment of anxiety in geriatric patients. *Curr Ther Res* 1984;35(1):100-112.

Xanax® 0.25 mg Tablets
alprazolam Ⓒ IV

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Please see adjacent page for brief summary of prescribing information.

XANAX® Tablets
(alprazolam) ©

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, eg, drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes of unknown significance have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

B-4-S

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I-5963
January 1986

Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ABNORMAL PULMONARY CIRCULATION—Volume 4 in CONTEMPORARY ISSUES IN PULMONARY DISEASE—Edited by Edward H. Bergofsky, MD, Professor of Medicine and Head, Pulmonary/Critical Care Division, Health Sciences Center, State University of New York at Stony Brook. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 335 pages, $45.

ABORTION, MEDICINE AND THE LAW—3rd Edition—Edited by J. Douglas Butler, DPM, JD, Dept of Orthopaedics, Howard County General Hospital, Maryland, and David F. Walbert, JD, Adjunct Professor of Law, Emory University, Atlanta. Facts On File Publications, 460 Park Ave South, New York, NY 10016, 1986. 755 pages, $40.

ABORTION: THE CONTINUING CONTROVERSY—Edited by Carol C. Collins and Oliver Trager. Facts On File Publications, 460 Park Avenue South, New York, NY 10016, 1986. 183 pages, $24.95.

ACUTE PAIN MANAGEMENT—Volume 8 in Clinics In Critical Care Medicine—Edited by Michael J. Cousins, MB, BS, MD, FFARACS, FFARCS, Professor and Chairman, and Garry D. Phillips, MB, BS, BSc (Med), FFARACS(INTENS), Director of Intensive Care, and Accident and Emergency, and Deputy Chairman, Department of Anaesthesia and Intensive Care, Flinders Medical Centre, The Flinders University of South Australia School of Medicine, Bedford Park, South Australia. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 290 pages, $34.

ANESTHESIA: SECOND EDITION—3 Volumes—Edited by Ronald D. Miller, MD, Professor and Chairman of Anesthesia, Professor of Pharmacology, Department of Anesthesia, University of California, San Francisco, School of Medicine, San Francisco. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 2,419 pages, $150.

ANESTHESIA FOR THE UNINTERESTED—Second Edition—Edited by John D. Tolmie, MD, Associate Professor of Anesthesia and Associate Dean of Student Affairs, Wake Forest University Medical Center, Bowman Gray School of Medicine, Winston-Salem, NC, and Alexander A. Birch, MD, Staff Anesthesiologist, Good Samatarian Hospital, Corvallis, Ore. Aspen Publishers Inc, 1600 Research Blvd, Rockville, MD 20850, 1986. 256 pages, $19.95 (paperback).

ANNUAL REVIEW OF NEUROSCIENCE—Volume 9, 1986—Edited by W. Maxwell Cowan, MD, Salk Institute for Biological Studies; Eric M. Shooter, MD, Stanford University School of Medicine; Charles F. Stevens, MD, Yale University School of Medicine, and Richard F. Thompson, MD, Stanford University. Annual Reviews Inc, 4139 El Camino Way, Palo Alto, CA 94306, 1986. 512 pages, $31.

ATLAS OF DRUG REACTIONS—R. Douglas Collins, MD, formerly Associate Clinical Professor of Medicine, University of Florida College of Medicine, Gainesville, and formerly Director, Internal Medicine Residency Program, Pensacola Foundation for Education and Research, Inc (PEP), Pensacola, Florida. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 410 pages, $55.

ATLAS OF STAPLING TECHNIQUES—Pedro A. Rubio, MD, PhD, Chief, Department of Surgery, Medical Center Del Oro Hospital, and Clinical Faculty of Surgery, University of Texas Health Science Center at Houston; with illustrations by Timothy H. Phelps, MS, Department of Medical Illustration, Baylor College of Medicine, Houston. Aspen Publishers Inc, 1600 Research Blvd, Rockville, MD 20850, 1986. 338 pages, $95.

BASIC DOPPLER ECHOCARDIOGRAPHY—Volume 17 in CLINICS IN DIAGNOSTIC ULTRASOUND—Edited by Joseph Kisslo, MD, Associate Professor of Medicine; David Adams, RCPT, RDMS, Chief Echocardiography Technician, and Daniel B. Mark, MD, MPH, Associate in Medicine (Cardiology), Duke University Medical Center, Durham, North Carolina. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 208 pages, $32.

BASIC SURGERY—Second Edition—Edited by John A. McCredie, MCh(Belf), FRCS(Eng & Edin), FRCS(C), FACS, Professor of Surgery and Professor of Therapeutic Radiology, University of Western Ontario, and Member, General Surgical Staff, Victoria Hospital, London, Ontario, and Gerard P. Burns, MCh(Belf), FRCS(Eng & Edin), FACS, Professor of Surgery, State University of New York at Stony Brook School of Medicine, and Senior Attending Surgeon, Long Island Jewish Medical Center, New Hyde Park, New York. Macmillan Publishing Co, 866 Third Ave, New York, NY 10022, 1986. 634 pages, $29.95 (paperback).

BEHAVIORAL NEUROLOGY—A PRACTICAL APPROACH—Volume 7 in Clinical Neurology and Neurosurgery Monographs—Howard S. Kirshner, MD, Associate Professor and Vice Chairman, Department of Neurology, and Associate Professor, Division of Hearing and Speech Sciences, Vanderbilt University School of Medicine; Director, Adult Neurology Services, and Associate Director, Rehabilitation Service, Vanderbilt University Hospital, Nashville, Tennessee. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 213 pages, $28.50.

BREAST DISEASE—Volume 1 in CONTEMPORARY ISSUES IN OBSTETRICS AND GYNECOLOGY—Edited by Douglas J. Marchant, MD, Professor of Obstetrics and Gynecology and Professor of Surgery, Tufts University School of Medicine, Boston. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 164 pages, $37.

CASE STUDIES IN PEDIATRIC EMERGENCY MEDICINE—Edited by Anthony J. Haftel, MD, Director, Division of Emergency Medicine, Childrens Hospital of Los Angeles. Aspen Publishers Inc, 1600 Research Blvd, Rockville, MD 20850, 1986. 287 pages, $33.50.

CLINICAL CARDIOLOGY—4th Edition—Maurice Sokolow, MD, Professor of Medicine Emeritus, Senior Staff Member, and Malcolm B. McIlroy, MD, Professor of Medicine and Senior Staff Member, Cardiovascular Research Institute, University of California, San Francisco. Lange Medical Publications, Los Altos, CA 94022, 1986. 631 pages, $26.50 (paperback).

THE CONSEQUENCES OF CHROMOSOME IMBALANCE—PRINCIPLES, MECHANISMS AND MODELS—Charles J. Epstein, MD, Professor of Pediatrics and Biochemistry, University of California, San Francisco. Cambridge University Press, 32 E 57th St, New York, NY 10022, 1986. 475 pages, $59.50.

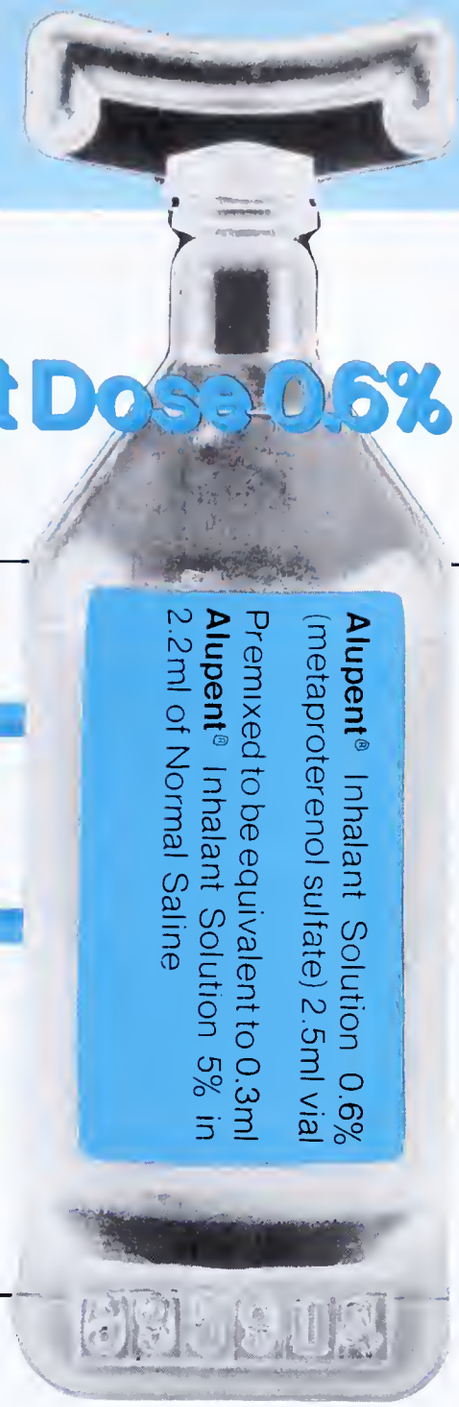
Jow on MEDI-CAL formulary

Alupent® Solution Unit Dose 0.6%

metaproterenol sulfate)

Bronchodilator

Medi-Cal Number : **1031F-CC**



- Up to six hours of bronchodilator efficacy
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- No metabisulfites

pent®
aproterenol sulfate)

Inhalant Solution
Unit-Dose Vial
Bronchodilator

Summary of Prescribing Information

CATIONS AND USAGE Alupent® (metaproterenol sulfate) Inhalant ion is indicated as bronchodilator for bronchial asthma and for sible bronchospasm which may occur in association with bronchitis mphysema

TRAINDICATIONS Use in patients with cardiac arrhythmias asso- d with tachycardia is contraindicated

ugh rare, immediate hypersensitivity reactions can occur. Therefore, ent (metaproterenol sulfate) Inhalant Solution, 0 6% is contraindicated ients with a history of hypersensitivity to any of its components.

NINGS Excessive use of adrenergic aerosols is potentially dan- us Fatalities have been reported following excessive use of Alupent aproterenol sulfate) as with other sympathomimetic inhalation arations, and the exact cause is unknown. Cardiac arrest was noted eral cases

doxical bronchoconstriction with repeated excessive administration een noted with sympathomimetic agents.

nts should be advised to contact their physician in the event that they t respond to their usual dose of sympathomimetic amine aerosol

CAUTIONS Because Alupent (metaproterenol sulfate) Inhalant Solu- a sympathomimetic drug, it should be used with great caution in nts with hypertension, coronary artery disease, congestive heart , hyperthyroidism or diabetes, or when there is sensitivity to sympa- metic amines.

mation for Patients Extreme care must be exercised with respect to dministration of additional sympathomimetic agents. A sufficient al of time should elapse prior to administration of another sympatho- tic agent.

nogenesis Long-term studies in mice and rats to evaluate the oral nogenic potential of metaproterenol sulfate have not been completed es of metaproterenol sulfate have not been conducted to determine genic potential or effect on fertility

nancy *Teratogenic Effects: Pregnancy Category C.* Alupent (meta- proterenol sulfate) has been shown to be teratogenic and embryocidal in rabbits when given orally in doses 620 times the human inhalation dose There are no adequate and well-controlled studies in pregnant women. Alupent should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Oral reproduction studies in mice, rats and rabbits showed no teratogenic or embryocidal effects at 50 mg/kg corresponding to 310 times the human inhalation dose Teratogenic effects in the rabbit included skeletal abnormalities and hydrocephalus with bone separation

Nursing Mothers It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Alupent (metaproterenol sulfate) is administered to a nursing woman

Pediatric Use Safety and effectiveness in children below the age of 12 have not been established

ADVERSE REACTIONS Adverse reactions are similar to those noted with other sympathomimetic agents

The most frequent adverse reactions to Alupent (metaproterenol sulfate) are nervousness and tachycardia which occur in about 1 in 7 patients, tremor which occurs in about 1 to 20 patients and nausea which occurs in about 1 in 50 patients. Less frequent adverse reactions are hypertension, palpitations, vomiting and bad taste which occur in approximately 1 in 300 patients

HOW SUPPLIED Alupent (metaproterenol sulfate) Inhalant Solution Unit Dose Vials are supplied as 0.6% clear colorless or nearly colorless solution, each vial containing 2.5 ml, with 25 vials per box. Do not use the solution if it is brown or has a precipitate.

Consult package insert before prescribing AL-UD-BPI-5/86

Boehringer Ingelheim

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★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

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FOR APPROPRIATE PATIENTS WITH MILD TO MODERATE HYPERTEN

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VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product.

NTIHYPERTENSIVE THERAPY

- Certain subjective symptoms such as malaise and drowsiness, which may interfere with physical or mental activity, have not been characteristic of VASOTEC. This may be related to the specificity of action of VASOTEC on the renin-angiotensin-aldosterone system.

- In worldwide controlled clinical trials, VASOTEC was generally well tolerated. The overall percentage of patients reporting adverse effects was comparable to placebo.

- For the most part, adverse effects in clinical trials were mild and transient and usually did not require discontinuation of therapy.

Angioedema has been reported in patients treated with angiotensin-converting-enzyme inhibitors, including VASOTEC (0.2% of patients treated with VASOTEC). Angioedema associated with laryngeal edema and/or shock may be fatal. **If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately** (see ADVERSE REACTIONS).

Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. Therefore, discontinue therapy with a beta blocker only in accordance with the recommendations in the prescribing information for that product. Begin therapy with VASOTEC on the day following the last day of therapy with the beta blocker.

FOR MANY HYPERTENSIVE PATIENTS

ONCE-A-DAY

VASOTEC®

(ENALAPRIL MALEATE | MSD)

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For a Brief Summary of Prescribing Information, please see next page of this advertisement.

FOR MANY HYPERTENSIVE PATIENTS

ONCE-A-DAY

VASOTEC®

(ENALAPRIL MALEATE | MSD)

Contraindications: VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product.

Warnings: *Angioedema:* Angioedema has been reported in patients treated with angiotensin-converting-enzyme inhibitors, including VASOTEC. Angioedema associated with laryngeal edema and/or shock may be fatal. **If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased.

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Neutropenia/Agranulocytosis: Another angiotensin-converting-enzyme inhibitor has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General: Impaired Renal Function:* In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of VASOTEC and/or discontinuation of the diuretic may be required.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia. (See *Drug Interactions.*)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, tongue, difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions.

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release. The antihypertensive effect of VASOTEC® (Enalapril Maleate, MSD) is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC may attenuate potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalaprif (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril, but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

There are no adequate and well-controlled studies in pregnant women. VASOTEC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2677 patients.

The most frequent clinical adverse experiences in controlled trials were: headache (4.8%), dizziness (4.6%), and fatigue (2.8%). For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences was not related to total daily dosage within the range of 10 to 40 mg. The overall percentage of patients treated with VASOTEC reporting adverse experiences was comparable to placebo.

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.6%), rash (1.5%), hypotension (1.4%), cough (1.3%), nausea (1.3%), and orthostatic effects (1.3%).

Clinical adverse experiences occurring in 0.5% to 1.0% of patients in the controlled trials included:

Cardiovascular: Syncope, orthostatic hypotension, palpitations, chest pain.

Nervous System: Insomnia, nervousness, paresthesia, somnolence.

Gastrointestinal System: Abdominal pain, vomiting, dyspepsia.

Other: Dyspnea, muscle cramps, hyperhydrosis, impotence, pruritus, asthenia.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema and/or shock may be fatal. If angioedema of the face, tongue, or glottis occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately (See WARNINGS.)

Hypotension: Combining the results of clinical trials in patients with hypertension or congestive heart failure, hypotension (including postural hypotension and other orthostatic effects) was reported in 2.3% of patients following the initial dose of enalapril or during extended therapy. In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. (See WARNINGS.)

Clinical Laboratory Test Findings:

Hyperkalemia: (See PRECAUTIONS.)

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.)

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in hypertensive patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

In overseas marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

For more detailed information, consult your MSD representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

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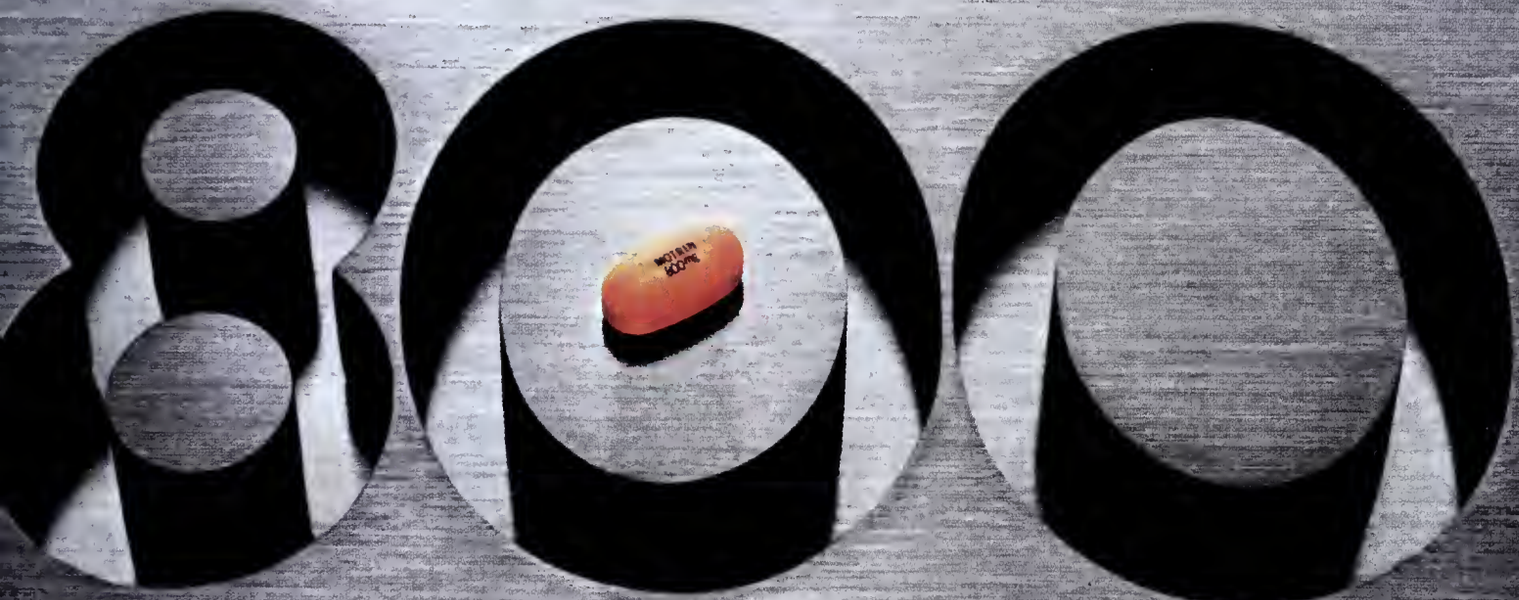

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

October 31-November 2—**Sixth Annual Southwestern Poison and Drug Information Symposium.** Scottsdale Sheraton Resort, Scottsdale. Friday-Sunday. Contact: U of A.

November 3-6—**Update in Clinical Medicine.** Sheraton Scottsdale Resort, Scottsdale. Monday-Thursday. Contact: American College of Physicians, (800) 523-1546

November 14-16—**Fifteenth Annual Radiology Seminar.** Marriott's Camelback Inn, Scottsdale. Friday-Sunday. Contact: Alex Newman, MD, Maricopa Medical Center, (602) 267-5361.

November 24-26—**Uncemented Total Joint Replacement.** Monday-Wednesday. Contact: Christine Campbell for St. Luke's Medical Center, (602) 947-7756.

February 12-15—**Arizona Academy of Family Physicians Scientific Assembly—1987.** Scottsdale Hilton, Scottsdale. Thursday-Sunday. Contact AAFP, (602) 249-2021.

Feburary 13-15—**Anesthesia for the 80s.** La Paloma Resort, Tucson. Friday-Sunday. Contact: Beverly Richter for Arizona Society of Anesthesiologists, (602) 246-8901.

February 18-21—**Crises and Controversies in Pediatrics.** Doubletree Inn, Tucson. Wednesday-Saturday. Contact: U of A.

February 19—**First Annual Interventional Angiography Symposium.** Thursday. Contact: Christine Campbell for St. Luke's Medical Center, (602) 947-7756.

February 22-25—**First Annual Barrow Neurological Institute Magnetic Resonance Imaging Conference.** Mountain Shadows Resort, Scottsdale. Sunday-Wednesday. Contact: Barrow Neurological Institute, (602) 285-3178 or (800) BARROW1.

February 25-27—**Tenth Annual Mid-Winter Symposium in OB/GYN.** Scottsdale Hilton, Scottsdale. Wednesday-Friday. Contact: Maricopa Medical Center, (602) 267-5444.

February 26-28—**Neurology and Neurosurgery of the Aging.** Mountain Shadows Resort, Scottsdale. Thursday-Saturday. Contact: Barrow Neurological Institute, (602) 285-3178 or (800) BARROW1.

PATHOLOGY

November 15-16—**Tumors of the Thyroid Gland and Head and Neck Tumors.** Arizona Society of Pathologists and U of A at Scottsdale Hilton, Scottsdale. Saturday-Sunday. 7 hrs. Contact: Beverly Richter, Arizona Society of Pathologists, 810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6173.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

October 27-31—**The Western Society of Allergy and Immunology's 25th Annual Session.** Marriott

(Continued on Page 459)

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Specialty	1986 CAP/MPT Estimated Cost*
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Cardiology with invasive vascular procedures	9,153
Cardiology — no invasive vascular procedures	4,393
Dermatology — no radiation or hair transplants	4,393
Gastroenterology with endoscopy and ERCP, board certified	6,773
Family Practice — no surgery	4,393
Family Practice — minor surgery or assisting at surgery	6,773
Family Practice — major surgery	14,991
General Surgery	14,991
Internal Medicine with invasive vascular procedures	9,153
Internal Medicine — no invasive vascular procedures	4,393
Neurology	2,012
Ophthalmology with surgery or laser	6,773
Orthopedics with spinal surgery	18,449
Orthopedics — no spinal surgery	16,719
Otolaryngology— doing plastic surgery, board certified	14,991
Pediatrics — General	2,012
Pediatrics — General, with invasive vascular procedures	9,153
Plastic Surgery, board certified	14,991
Psychiatry — no electro-convulsive therapy	2,012
Radiology — diagnostic, no coronary angiography	4,393
Radiology — including coronary angiography	9,153
Urology	11,533

*These rates include dues and assessments for a CAP/MPT member with 50 or more months of membership or retroactive coverage (matured rate). CAP/MPT offers coverage limits of $1 million per occurrence with an aggregate of $3 million per year.

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ACE* INHIBITOR

capozide®

CAPTOPRIL–HYDROCHLOROTHIAZIDE TABLETS

OUTSTANDING SINGLE-TABLET BLOOD PRESSURE CONTROL†

- Pressure normalized‡ at six months in 86% of patients with mild-to-moderate hypertension (N = 53).§[1]
- Additive antihypertensive effect achieved through complementary actions of ACE inhibition plus thiazide diuresis.
- Convenient, one-tablet bid dosage regimen enhances compliance.

*Angiotensin Converting Enzyme

†**This fixed combination drug is not indicated for initial therapy of hypertension. It may be appropriate if the fixed combination represents the dosage as titrated to the individual patient's needs. In using CAPOZIDE, consideration should be given to the risk of neutropenia/agranulocytosis. Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. See INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, and ADVERSE REACTIONS in the brief summary, which follows.**

‡Normalized = diastolic pressure < 91 mm Hg.

§Dosage was CAPOZIDE 25/25 (captopril 25 mg and hydrochlorothiazide 25 mg per tablet) bid.

WITH BUILT-IN POTASSIUM-SPARING ACTIVITY

- ACE inhibition conserves potassium by minimizing aldosterone secretion —can reduce thiazide-induced hypokalemia.

- In a multicenter clinical study, CAPOZIDE blunted the decrease in serum potassium that was seen with hydrochlorothiazide alone.[2]

ACE INHIBITOR*

capozide®

CAPTOPRIL–HYDROCHLOROTHIAZIDE TABLETS
25/15, 25/25, 50/15, 50/25

HELPS KEEP POTASSIUM UP, BLOOD PRESSURE DOWN

*Angiotensin Converting Enzyme

References:
1. Lederle RM: Captopril and hydrochlorothiazide in the fixed combination multicenter trial. J Cardiovasc Pharmacol 7:S63–S69, 1985.
2. Weinberger MH: Influence of an angiotensin converting-enzyme inhibitor on diuretic-induced metabolic effects in hypertension. Hypertension 5(Suppl III):132S–138S, 1983.

Please see brief summary of prescribing information on adjacent page.

CAPOZIDE®
Captopril-Hydrochlorothiazide Tablets

INDICATIONS AND USAGE:—CAPOZIDE (Captopril-Hydrochlorothiazide Tablets) is indicated for the treatment of hypertension. **This fixed combination drug is not indicated for initial therapy of hypertension. If the fixed combination represents the dose titrated to the individual patient's needs, it may be more convenient than the separate components.** In using CAPOZIDE, consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOZIDE may be used for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, CAPOZIDE should be reserved for hypertensives who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to other drug combinations.

CONTRAINDICATION: Hydrochlorothiazide—Hydrochlorothiazide is contraindicated in patients with anuria and those who have previously demonstrated hypersensitivity to hydrochlorothiazide or other sulfonamide-derived drugs.

WARNINGS: Captopril—Neutropenia/Agranulocytosis—Neutropenia (<1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine <1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. Of reported cases, about half had serum creatinine ≥1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present. Neutropenia has appeared within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria—Total urinary proteins >1 g/day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy, patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

Hydrochlorothiazide—Use with caution in severe renal disease. May precipitate azotemia in patients with renal disease. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

PRECAUTIONS: General: Captopril—*Impaired Renal Function*—Some patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible (see DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]). *Surgery/Anesthesia*—If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Hydrochlorothiazide—Observe all patients for signs of fluid or electrolyte imbalance, particularly when the patient is vomiting excessively or receiving parenteral fluids. Warning signs include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and nausea and vomiting. Hypokalemia may develop when severe cirrhosis is present or without adequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of the heart to the toxic effects of digitalis. Because captopril reduces the production of aldosterone, concomitant therapy with captopril reduces the diuretic-induced hypokalemia. Fewer patients may require potassium supplements and/or foods with a high potassium content (see Drug Interactions, Agents Increasing Serum Potassium).

Any chloride deficit is generally mild and may not require specific treatment, exceptions include liver disease or renal disease. Dilutional hyponatremia may occur in edematous patients in hot weather; use water restriction, rather than salt administration except when the hyponatremia is life-threatening. In actual salt depletion, replacement is the therapy of choice. Hyperuricemia may occur or frank gout may be precipitated in certain patients. Latent diabetes mellitus may become manifest. Antihypertensive effects may be enhanced in the postsympathectomy patient. Progressive renal impairment, indicated by rising nonprotein nitrogen or blood urea nitrogen, requires a careful reappraisal of the necessity of therapy. Serum PBI levels may decrease. Calcium excretion is decreased. Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed during prolonged therapy.

Laboratory Tests—Serum and urine electrolyte levels should be regularly monitored (see WARNINGS, [Captopril and Hydrochlorothiazide], also PRECAUTIONS [General, Hydrochlorothiazide]).

Drug Interactions—Captopril—*Hypotension—Patients on Diuretic Therapy:* Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose. *Agents Having Vasodilator Activity:* In heart failure patients, vasodilators should be administered with caution. *Agents Causing Renin Release:* Captopril's effect will be augmented by antihypertensive agents that cause renin release. *Agents Affecting Sympathetic Activity:* The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution. *Agents Increasing Serum Potassium:* Give potassium sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution. *Inhibitors Of Endogenous Prostaglandin Synthesis:* Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Hydrochlorothiazide—When administered concurrently the following drugs may interact with thiazide diuretics: *Alcohol, barbiturates, or narcotics*—potentiation of orthostatic hypotension may occur. *Antidiabetic drugs (oral agents and insulin)*—Hyperglycemia induced by thiazides may require dosage adjustment of the antidiabetic drug. *Other antihypertensive drugs*—additive effect or potentiation. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. *Corticosteroids, ACTH*—intensified electrolyte depletion, particularly hypokalemia. *Preanesthetic and anesthetic agents*—effects of preanesthetic and anesthetic agents may be potentiated; adjust dosage of these agents accordingly. *Pressor amines (e.g., norepinephrine)*—possible decreased response to pressor amines but not sufficient to preclude their use. *Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)*—possible increased responsiveness to the muscle relaxant. *Lithium*—should not generally be given with diuretics; diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with CAPOZIDE.

Drug/Laboratory Test Interactions—Captopril—may cause a false-positive urine test for acetone.

Hydrochlorothiazide—Discontinue thiazides before carrying out tests for parathyroid function (see PRECAUTIONS [General, Hydrochlorothiazide]).

Carcinogenesis, Mutagenesis and Impairment of Fertility—Captopril—Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Hydrochlorothiazide—Long-term studies in animals have not been performed to evaluate carcinogenic potential, mutagenesis, or whether this drug affects fertility in males or females.

Pregnancy: Category C—Captopril—There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniotacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Hydrochlorothiazide—Studies in pregnant rats using captopril and hydrochlorothiazide individually and in combination, each agent in doses up to 1350 mg/kg, failed to show evidence of embryotoxicity, fetotoxicity, or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CAPOZIDE should be used during pregnancy, or in patients likely to become pregnant, only if the potential benefit justifies the potential risk to the fetus.

Pregnancy—Nonteratogenic Effects—Hydrochlorothiazide—Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the benefit be weighed against possible hazards to the fetus. Hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other reported reactions.

Nursing Mothers: Both captopril and hydrochlorothiazide are excreted in human milk. A potential exists for serious adverse reactions in nursing infants from both drugs, therefore, decision whether to discontinue nursing or to discontinue therapy should take into account the importance of CAPOZIDE (Captopril-Hydrochlorothiazide Tablets) to the mother.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. CAPOZIDE should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Captopril—Reported incidences are based on clinical trials involving approximately 7000 patients. *Renal*—About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients. *Hematologic*—Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported. *Dermatologic*—Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients. *Cardiovascular*—Hypotension may occur, see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients. *Dysgeusia*—About 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Hydrochlorothiazide—*Gastrointestinal System*—anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, and sialadenitis. *Central Nervous System*—dizziness, vertigo, paresthesias, headache, and xanthopsia. *Hematologic*—leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, and hemolytic anemia. *Cardiovascular*—orthostatic hypotension. *Hypersensitivity*—purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis; cutaneous vasculitis), fever, respiratory distress including pneumonitis, and anaphylactic reactions. *Other*—hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, and transient blurred vision. Whenever adverse reactions are moderate or severe, reduce or withdraw therapy.

Altered Laboratory Findings: Elevations of liver enzymes have been noted in a few patients but no causal relationship to captopril use has been established. Rare cases of cholestatic jaundice and of hepatocellular injury with or without secondary cholestasis have been reported in association with captopril administration. A transient elevation of BUN and serum creatinine may occur, especially in patients who are volume-depleted or who have renovascular hypertension. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in the serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Captopril—Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

Hydrochlorothiazide—In addition to diuresis, overdosage of thiazides may produce varying degrees of lethargy which may progress to coma within a few hours, with minimal respiratory and cardiovascular depression and without evidence of serum electrolyte changes or dehydration. The mechanism of thiazide-induced CNS depression is unknown. Gastrointestinal irritation and hypermotility may occur. Transitory increase in BUN has been reported, and serum electrolyte changes may occur, especially in patients with impaired renal function. In addition to gastric lavage and supportive therapy for stupor or coma, symptomatic treatment of gastrointestinal effects may be needed. Degree of removal by hemodialysis has not been clearly established. Measures to maintain hydration, electrolyte balance, respiration, and cardiovascular and renal function should be instituted.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED (SEE INDICATIONS AND USAGE). CAPOZIDE (Captopril-Hydrochlorothiazide Tablets) should be taken one hour before meals. CAPOZIDE may be dosed bid or tid. Because captopril and hydrochlorothiazide are excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOZIDE (Captopril-Hydrochlorothiazide Tablets). Available in tablets of 25 mg captopril combined with 15 mg hydrochlorothiazide, 25 mg captopril combined with 25 mg hydrochlorothiazide, 50 mg captopril combined with 15 mg hydrochlorothiazide, and 50 mg captopril combined with 25 mg hydrochlorothiazide in bottles of 100.
(J4-005C)

SQUIBB® INNOVATORS IN CARDIOVASCULAR MEDICINE

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(Continued from Page 454)

Hotel, Maui, Hawaii. Monday-Friday. Contact: Joyce Gullixson, 1700 SW Columbia, Portland, OR 97201. (503) 224-6159.

December 21-27—**Allergy, Immunology and the Practicing Physician—"Christmas '86—Maui."** Hawaii Medical Association at Royal Lahaina Resort, Kaanapali Beach, Maui. One week. 18 hrs. Fee: $385. Contact: Joe Harrison, MD, Symposium Maui, Inc, PO Box 10185, Lahaina, HI 96761. (808) 879-8182 or 661-8032.

ANESTHESIOLOGY

October 17-21—**American Society of Anesthesiologists Annual Meeting.** Las Vegas Convention Center. Friday-Tuesday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068. (312) 825-5586.

October 22-28—**Post-ASA Annual Meeting.** California Society of Anesthesiologists at Maui Inter-Continental Hotel, Hawaii. Wednesday-Tuesday. 20 hrs. Contact: Linda P. Londerville, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

January 8-11—**Anesthesia Update—1987.** UCSD at Hotel Inter-Continental, San Diego. Thursday-Sunday. 20 hrs. Contact: UCSD.

January 30—February 1—**25th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Marriott Hotel, Los Angeles. Friday-Sunday. 15 hrs. Fee: $175. Contact: Wayne Herbert, MD, Children's Hospital of Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

February 8-12—**15th Obstetric Anesthesia Conference.** Ohio State University Hospital at Sheraton Waikiki Hotel, Hawaii. Sunday-Thursday. Contact: Ohio State University Hospital, Dept of Anesthesiology, 410 W 10th Ave, Columbus, OH 43210. (614) 421-8487.

CANCER

October 17—**New Modalities in Cancer Therapy.** Memorial Regional Cancer Center, Modesto. Friday. 6 hrs. Contact: Janice Jarboe, Education Dept, Memorial Hospitals Assoc, PO Box 942, Modesto 95353. (209) 526-4500, ext 6680.

October 27-29—**10th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Island Hotel East, San Diego. Monday-Wednesday. 22 hrs. Fee: $350. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy, San Diego 92121. (619) 453-6222.

December 5-6—**Recent Advances in Occupational Cancer.** UCSF at Cathedral Hill Hotel, San Francisco. Friday-Saturday. 13 hrs. Fee: $200. Contact: UCSF.

February 16-18—**Clinical Hematology and Oncology—1987.** Scripps Clinic, La Jolla at Vacation Village Resort, San Diego. Monday-Wednesday. Contact: Bonny Mower, Dept of Academic Affairs, Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

March 12-14—**2nd International Conference on Monoclonal Antibody Immunoconjugates for Cancer.** UCSD at Hotel Inter-Continental, San Diego. Thursday-Saturday. Contact: UCSD.

CARDIOLOGY

October 16-18—**10th Annual Cardiology Update—1986.** American College of Cardiology at Quail Lodge, Carmel. Thursday-Saturday. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 227.

October 17-18—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Desert Inn Hotel, Las Vegas, Nevada. Friday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

October 24-26—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

October 25—**9th Annual Northridge Hospital Medical Center Heart Symposium.** Center Plaza Hotel, Los Angeles. Saturday. 6 hrs. Fee: $120. Contact: Dept of Medical Education, Northridge Hospital Medical Center, 18300 Roscoe Blvd, Northridge 91328. (818) 885-5311.

November 1—**The Heart and the Brain: Clinical Interrelationships—Office Management of Stress and Emotionally Induced Cardiovascular Disabilities.** UCI at Center for Health Education, Long Beach. Saturday. Contact: UCI.

November 12—**Pulmonary and Intensive Care Medicine.** LLU at LLU. Wednesday. 5 hrs. Fee: $60. Contact: LLU.

December 5-6—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Bally's (MGM) Grand Hotel, Las Vegas, Nevada. Friday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

December 5-7—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Caesars Palace, Las Vegas, Nevada. Friday-Sunday. 13 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

December 12-13—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Americana Canyon Hotel, Palm Springs. Friday-Saturday. 11 hrs. Fee: $295. Contact: Medical Education Resources, Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or in Colorado (303) 798-9682.

December 12-14—**Advances in Heart Disease.** American College of Cardiology at Hyatt Regency on Union Square, San Francisco. Friday-Sunday. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 227.

January 23-25—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

January 29-31—**Cardiology '87.** Scripps Memorial Hospital, La Jolla at La Jolla Marriott Hotel, San Diego. Thursday-Saturday. 18 hrs. Fee: $275. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 29-31—**Clinical Nuclear Cardiology: Case Review with the Experts.** American College of Cardiology at Cedars-Sinai Medical Center, Los Angeles. Thursday-Saturday. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400.

February 4-7—**4th Annual Cardiopulmonary Conference.** American College of Chest Physicians at Lake Tahoe. Wednesday-Saturday. Contact: ACCP, 911 Busse Highway, Park Ridge, IL 60068. (312) 698-2200 or (916) 739-8833.

February 5-8—**Pathophysiology and Techniques of Cardiopulmonary Bypass: VII.** Cardiothoracic Research and Education Foundation at Sheraton Island East Hotel, San Diego. Thursday-Sunday. 15 hrs. Fee: $300. Contact: CREF, PO Box 33185, San Diego 92103. (619) 692-9115.

February 6-7—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Bally's (MGM) Grand Hotel, Las Vegas, Nevada. Friday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

February 9-13—**2nd Annual Cardiovascular Conference.** American College of Cardiology at Sheraton Royal Waikaloa Hotel, Kona Coast, Hawaii. Monday-Friday. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 227.

February 13-14—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Americana Resort Hotel, Palm Springs. Friday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

March 22-25—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Royal Lahaina Hotel, Maui, Hawaii. Sunday-Wednesday. 13 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

March 27-28—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Desert Inn Hotel, Las Vegas, Nevada. Friday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

(Continued on Page 466)

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for healed duodenal ulcer patients

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In two randomized, double-blind, and well-controlled clinical trials, ZANTAC 150 mg h.s. significantly superior to cimetidine 400 mg h.s. for maintenance therapy in healed duodenal ulcers.

Percent of patients with observed duodenal ulcer recurrence

		0-4 months	0-8 months	0-12 months	No. patients
USA[1]	ranitidine 150 mg h.s.	9%	14%*	16%†	60
	cimetidine 400 mg h.s.	23%	34%	43%	66
UK, Ireland, Australia[2]	ranitidine 150 mg h.s.	8%‡	14%‡	23%‡	243
	cimetidine 400 mg h.s.	21%	34%	37%	241

*p=0.02
†p=0.01
‡p≤0.004
%=life-table estimates
All patients were permitted prn antacids for relief of pain.

These two trials used the currently recommended dosing regimen of cimetidine (400 mg h.s.) and ranitidine (150 mg h.s.). A comparison of other dosing regimens has not been studied.

The studied dosing regimens are not equivalent with respect to the degree and duration of acid suppression or suppression of nocturnal acid.

The superiority of ranitidine over cimetidine in these trials indicates that the dosing regimen currently recommended for cimetidine is less likely to be as successful in maintenance therapy.

Convenient once-a-night dose with a low incidence of side effects[3]

Headache, sometimes severe, seems to be related to ranitidine administration. Other side effects have been reported; for a complete listing, see the **ADVERSE REACTIONS** section in the Brief Summary.

No significant interference with the hepatic cytochrome P-450 enzyme system at recommended doses

ZANTAC 150 mg has no significant drug interactions with theophylline, phenytoin, or warfarin. The bioavailability of certain medications whose absorption is dependent on a low gastric pH may be altered when ZANTAC or other medications that decrease gastric acidity are administered.

Zantac® 150
ranitidine HCl/Glaxo 150 mg tablets

One tablet at bedtime
for maintenance

See next page for references and
Brief Summary of Product Information.

Glaxo / ROCHE®

CONFIRMED

Zantac® 150

ranitidine HCl/Glaxo 150 mg tablets

One tablet at bedtime for maintenance therapy in healed duodenal ulcer patients

References:

1 Silvis SE, Griffin J, Hardin R, et al: Final report on the United States multicenter trial comparing ranitidine to cimetidine as maintenance therapy following healing of duodenal ulcer. *J Clin Gastroenterol* 1985;7(6):482-487.

2. Gough KR, Korman MG, Bardhan KD, et al: Ranitidine and cimetidine in prevention of duodenal ulcer relapse. A double-blind, randomised, multicentre, comparative trial. *Lancet* 1984,ii 659-662.

3. Data available on request, Glaxo Inc.

ZANTAC® 150 Tablets
(ranitidine hydrochloride)
ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY OF PRODUCT INFORMATION

See complete product information before prescribing. The following is a brief summary

INDICATIONS AND USAGE: ZANTAC® is indicated in:

1. Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks.

2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.

3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).

4 Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated

5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy. 2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function. Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day

Ranitidine was not mutagenic in standard bacterial tests *(Salmonella, E coli)* for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with oral ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Rare reports of reversible leukopenia, granulocytopenia, thrombocytopenia, and pancytopenia.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumental: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison Syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day

GERD: The current recommended adult oral dosage is 150 mg twice a day.

See full prescribing information for dosage adjustment for patients with impaired renal function.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

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June 1986

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(Continued from Page 460)

DERMATOLOGY

October 18—**Dermatology.** Kaiser Permanente Medical Group at Ramada Renaissance Hotel, Long Beach. Saturday. 7 hrs. Fee: $100. Contact: Judy Harrison, Dept of Clinical Services, Southern California Permanente Medical Group, 393 E Walnut St, Pasadena 91188. (818) 405-5000.

January 23-25—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** Continuing Medical Education Associates, San Diego. Friday-Sunday. 20 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

EMERGENCY MEDICINE

October 27-31—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Monday-Friday. 40 hrs. Fee: $550. Contact: UCSF.

October 27-31—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD at Hanalei Hotel, San Diego. Monday-Friday. Contact: UCSD.

October 31-November 2—**30th Annual Western Occupational Health Conference.** Western Occupational Medical Association at Golden Gateway Holiday Inn, San Francisco. Friday-Sunday. 14 hrs. Fee: $175. Contact: Joe Donovan, WOMA, 433 Palmer Ave, Aptos 95003. (408) 688-9667.

November 16—**Emergencies in Medical Practice.** Granada Hills Community Hospital at Sheraton Universal Hotel, North Hollywood. Sunday. 7 hrs. Fee: $100. Contact: Beverly Chaussee, Granada Hills Community Hospital, 10445 Balboa Blvd, Granada Hills 91344. (818) 360-1021, ext 6789.

December 7-13—**Current Concepts in Emergency Care.** American College of Emergency Physicians at Royal Lahaina Resort, Maui. Sunday-Saturday. 25 hrs. Contact: Georgine Elich, Kailani World Travel, 4192 Meridian Ave, Bellingham, WA 98226. USA (800) 426-2561 or in Washington (800) 562-2597.

December 8-12—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD. Monday-Friday. 32 hrs. Fee: $325-440. Contact: UCSD.

January 12-16—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD at San Diego Hilton Hotel. Monday-Friday. 32 hrs. Fee: $325-440. Contact: UCSD.

February 2-4—**Trauma Management—1987.** UCSD at Hotel Inter-Continental, San Diego. Monday-Wednesday. 20 hrs. Contact: UCSD.

March 16-20—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium II and Advanced Emergency Procedures Laboratory.** UCSD. Monday-Friday. 32 hrs. Fee: $325-440. Contact: UCSD.

INTERNAL MEDICINE

October 16-17—**Gene Probe Technology—From Theory to Practice.** UCSD at San Diego Hilton Beach and Tennis Club. Thursday-Friday. 9.5 hrs. Contact: Emily S. Winn-Deen, PhD, Behring Diagnostics, 10933 N Torrey Pines Rd, La Jolla 92037. (619) 450-5624

November 8-9—**Transurethral Ureteroscopy: A Seminar and Workshop.** UCSD at La Jolla Marriott Hotel, San Diego. Saturday-Sunday. 13.5 hrs. Fee: $375. Contact: UCSD.

November 8-10—**State of the Art Urology—Live Television Coverage of Surgery.** UCLA at Miramar Sheraton Hotel, Santa Monica. Saturday-Monday. 21 hrs. Fee: $400. Contact: UCLA.

November 10-12—**Selected Topics in Endocrinology and Metabolism.** LLU at Ahwahnee Hotel, Yosemite. Monday-Wednesday. 12 hrs. Fee: $225. Contact: LLU.

November 14-16—**Operative and Critical Care for Neurological Trauma and Disease.** UCSD at Hotel Inter-Continental, San Diego. Friday-Sunday. 19 hrs. Contact: Pat Curl, Unconventional, 3690 Park Blvd, Ste F, San Diego 92103. (619) 692-9115.

December 27-January 1—**Advances in Internal Medicine.** University of Washington at Kauai Sheraton, Kauai. Saturday-Thursday. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle 98195. (206) 543-1050.

January 14—**Urology Update.** LLU at LLU. Wednesday. 7 hrs. Fee: $60. Contact: LLU.

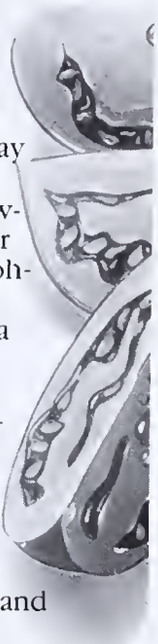
February 1-5—**Internal Medicine 1987: An Office Practice Review.** Sharp Memorial Hospital at Hotel Del Coronado, San Diego. Sunday-Thursday. 28 hrs. Fee: $395. Jackie Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

February 1-6—**Winter Urologic Forum.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sunday-Friday. 22 hrs. Fee: $370. Contact: UCD.

February 4-6—**Emerging Technology and Future Trends in Clinical Laboratory Molecular Analyses.** Scripps Clinic and Research Foundation at Vacation Village Resort, San Diego. Wednesday-Friday. 20 hrs. Contact: Bonny Mower, Dept of Academic Affairs, Scripps Clinic and Research Foundation, Box 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

(Continued on Page 563)

A defense against cancer can be cooked up in your kitchen.



There is evidence that diet and cancer are related. Some foods may promote cancer, while others may protect you from it.

Foods related to lowering the risk of cancer of the larynx and esophagus all have high amounts of carotene, a form of Vitamin A which is in cantaloupes, peaches, broccoli, spinach, all dark green leafy vegetables, sweet potatoes, carrots, pumpkin, winter squash, and tomatoes, citrus fruits and brussels sprouts.

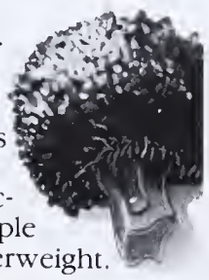
Foods that may help reduce the risk of gastrointestinal and respiratory tract cancer are cabbage, broccoli, brussels sprouts, kohlrabi, cauliflower.

Fruits, vegetables and whole-grain cereals such as oatmeal, bran and wheat may help lower the risk of colorectal cancer.

Foods high in fats, salt- or nitrite-cured foods such as ham, and fish and types of sausages smoked by traditional methods should be eaten in moderation.

Be moderate in consumption of alcohol also.

A good rule of thumb is cut down on fat and don't be fat. Weight reduction may lower cancer risk. Our 12-year study of nearly a million Americans uncovered high cancer risks particularly among people 40% or more overweight.



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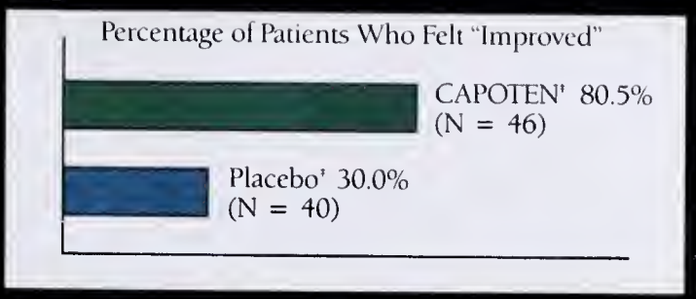
24.3% increase after 12 weeks of APOTEN versus 0.4% with digitalis nd diuretics alone.†[1]

8 out of 10 Patients Rated Themselves "Improved" with CAPOTEN[1]



☐ *Use CAPOTEN when symptoms persist despite digitalis and diuretic therapy.*

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ety-two patients, refractory to but continuing on digitalis and retics, were given CAPOTEN or placebo for 12 weeks. Patients e primarily New York Heart Association Class II and Class III. ages of CAPOTEN ranged from an initial 25 mg tid to a timum maintenance dosage of 100 mg tid.[1]

en with digitalis and diuretics.

POTEN is indicated in patients with heart failure who have not onded adequately to or cannot be controlled by conventional retic and digitalis therapy. CAPOTEN is to be used with retics and digitalis. In using CAPOTEN, consideration should be n to the risk of neutropenia/agranulocytosis. Use special autions in patients with impaired renal function, collagen ular disorders, or those exposed to other drugs (e.g., rainamide) known to affect the white cells or immune onse. Evaluation of heart failure patients should always ude assessment of renal function. See INDICATIONS, RNINGS, and ADVERSE REACTIONS in the brief summary he adjacent page.

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension—CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Neutropenia/Agranulocytosis—Neutropenia ($<1000/mm^3$) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine <1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count $<1000/mm^3$) withdraw captopril and closely follow the patient's course.

Proteinuria—Total urinary proteins >1 g/day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy, patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function,* Hypertension—Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction.

Surgery/Anesthesia—If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity—In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis—Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C—There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal—About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis have occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic—Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension may occur, see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—About 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg also available in bottles of 1000), and in UNIMATIC® single dose packs of 100 tablets. (J3-658D)

Reference. 1 Cannon PJ, Criley JM, Dzau VJ, et al: A placebo-controlled trial of captopril in refractory chronic congestive heart failure. J Am Col Cardiol 2:755–763, 1983.

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* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: **Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

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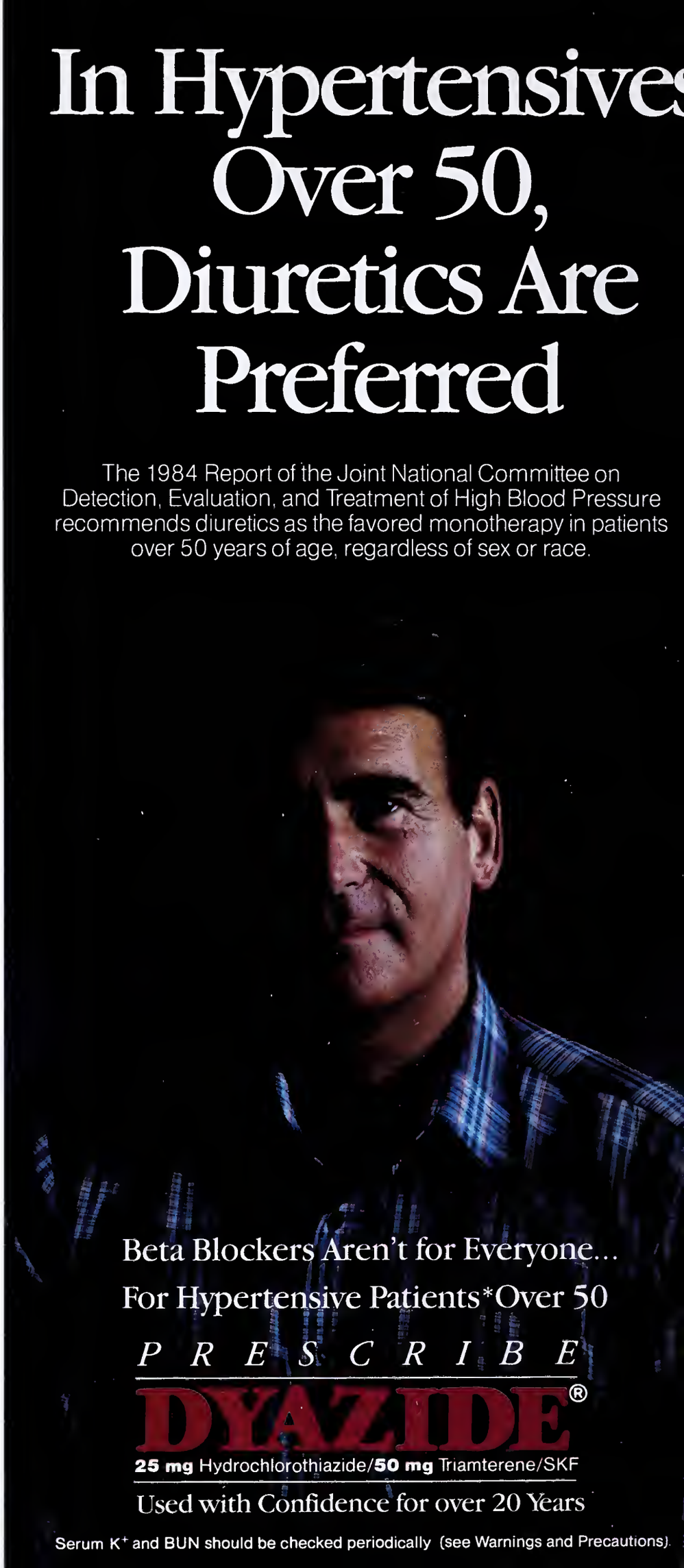

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Clinical Investigation

Exercise Tests and Ventricular Tachycardia

JULIO MILANES, MD; MARIO ROMERO, MD; HERBERT N. HULTGREN, MD, *and* UDIPI SHETTIGAR, MD, *Palo Alto, California*

All treadmill exercise tests done at the Palo Alto Veterans Administration Medical Center from 1973 to 1982 were reviewed to identify episodes of ventricular tachycardia (≥ 3 consecutive ventricular ectopic complexes) or ventricular fibrillation occurring during or within 8 minutes of cessation of symptom-limited exercise. Of patients with a clinical diagnosis of coronary artery disease (900 tests), ventricular tachycardia occurred in 36 (4.0%) and ventricular fibrillation in 6 (0.7%). Of patients without known coronary disease (1,700 tests), ventricular tachycardia occurred in 12 (0.07%), and no patient had ventricular fibrillation. Most arrhythmias ceased spontaneously and only 5 patients required cardioversion. We conclude that exercise tests are safe, the incidence of ventricular tachycardia or ventricular fibrillation is low—these arrhythmias occurring largely in patients with known coronary disease—spontaneous return to sinus rhythm is common and no deaths were associated with 2,400 consecutive tests.

(Milanes J, Romero M, Hultgren HN, et al: Exercise tests and ventricular tachycardia. West J Med 1986 Oct; 145:473-476)

Ventricular ectopic beats are commonly observed during exercise testing, especially in patients with coronary artery disease, and this phenomenon has been the focus of much research. Few studies have been made of the more serious ventricular arrhythmias induced by exercise. For this reason the present study was undertaken to examine the incidence, characteristics and prognostic significance of ventricular tachycardia and ventricular fibrillation occurring during diagnostic exercise testing.

Methods and Materials

All exercise tests done at the Palo Alto Veterans Administration Medical Center from 1973 to 1982 were reviewed to identify episodes of ventricular tachycardia or ventricular fibrillation occurring either during or within eight minutes of the cessation of exercise. All tests were done according to the Bruce multistage continuous treadmill protocol. Tests were stopped when significant symptoms, exertional hypotension or significant electrocardiographic (ECG) abnormalities appeared including pronounced ST depression or cardiac arrhythmias. Twelve-lead ECGs were recorded before each test. During exercise, two ECG leads (V_5 and lead II) were recorded at one-minute intervals and for 8 to 12 minutes after exercise. Ischemic ST changes were diagnosed when ST depression of 1 mm or more with a duration of 0.08 second or longer was present during or after the completion of exercise. β-Blocker and long-acting nitrate therapy was stopped the evening before the test. All tests were carried out on a Quinton treadmill (Quinton Instruments Company, Seattle). ECGs were recorded with a Hewlett Packard model 1151 B electrocardiograph (Hewlett Packard Corporation, Brisbane, California). Ventricular tachycardia was defined as three or more consecutive ectopic ventricular depolarizations that were classified as either unifocal or multifocal (Figures 1 and 2). Unifocal ventricular tachycardia of four beats or more (Figure 3) was evaluated separately. Ventricular fibrillation (Figure 4) was defined by conventional criteria. In all but one patient with ventricular fibrillation, the onset was similar to that shown in Figure 4—that is, rapid ventricular tachycardia or ventricular flutter deteriorating to ventricular fibrillation with a fine waveform.

All exercise test records were reviewed by a single observer to detect ventricular tachycardia or ventricular fibrillation. The prematurity of the first ventricular ectopic beat is expressed as the R-R′ interval—that is, the interval from the peak of the R wave of the last normal beat and the R wave peak of the ventricular premature beat. The QT interval was corrected for the heart rate by the formula of Bazett. The QT interval was measured in any lead where the exact QRS onset could be identified and the termination of the T wave was clearly evident.

The data base for this study consisted of 2,600 consecutive

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treadmill tests carried out over a nine-year period. The reason for doing the test and the clinical diagnoses were as follows: 1,200 tests (45%) were done to evaluate chest pain in patients without other evidence of cardiac disease; 900 tests (35%) were done in patients with known coronary artery disease, and 500 tests (20%) were done in patients with miscellaneous forms of heart disease. Follow-up data were obtained by mail or telephone in all patients with ventricular tachycardia of four beats or more and those who had ventricular fibrillation.

All data are expressed as mean values and one standard deviation. The significance of differences between groups was calculated by the χ^2 test and the two-sample t test for proportions and means, respectively.[1,2] A P value of .05 or less was considered significant.

Results

The incidence of ventricular fibrillation and tachycardia in two groups of patients is shown in Table 1. Ventricular fibrillation occurred only in patients with coronary artery disease. The incidence of ventricular tachycardia in patients with coronary artery disease was 4% compared with 0.07% in patients without coronary artery disease. Clinical characteristics of the 54 patients with ventricular tachycardia or fibrillation are shown in Tables 1, 2 and 3. Most of the patients had angina (87%) and coronary artery disease (78%). A normal resting ECG was present in 56%.

A comparison of the characteristics of ventricular tachycardia in patients with and without coronary artery disease is shown in Table 4. Only five characteristics were significantly different between the two groups. Patients with coronary artery disease had a higher heart rate preceding the arrhythmia, a shorter R-R′ interval, a higher prevalence of chest pain and more ischemic ST depression. Ventricular premature beats preceding ventricular tachycardia occurred more frequently in patients with coronary artery disease.

A special subgroup of patients was identified who exhibited ventricular tachycardia of four or more consecutive uni-

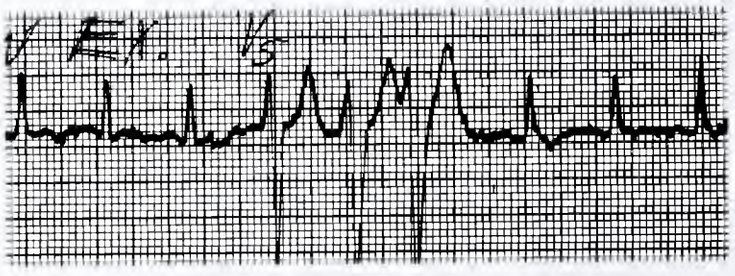

Figure 1.—Unifocal ventricular tachycardia of 3 consecutive beats.

Figure 2.—Multifocal ventricular tachycardia of 3 consecutive beats.

Figure 3.—Unifocal ventricular tachycardia of 11 consecutive beats.

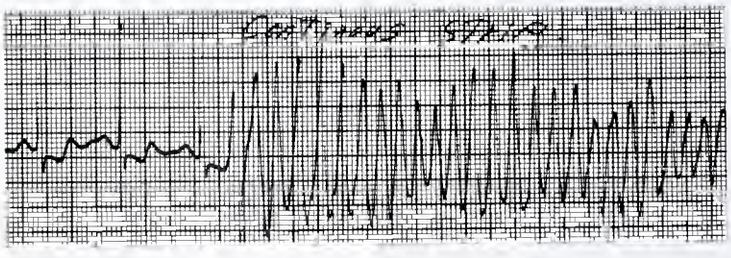

Figure 4.—Ventricular fibrillation: initial complexes suggest ventricular flutter with later deterioration to typical fibrillation.

TABLE 1.—*Incidence of Ventricular Tachycardia and Ventricular Fibrillation in the Patient Population*

Patient Population	Tachycardia, Percent (Number)	Fibrillation Percent (Number)
All treadmill tests, N = 2,600	1.9 (48)	0.2 (6)
Known CAD, N = 900	4.0 (36)	0.7 (6)
No known CAD, N = 1,700*	0.07 (12)	0 (0)

CAD = coronary artery disease

*Includes patients with miscellaneous forms of heart disease.

TABLE 2.—*Clinical Features of 54 Patients With Exercise-Induced Ventricular Tachycardia or Ventricular Fibrillation*

Clinical Features	Patients Number	Patients Percent
Symptoms		
Angina	47	87
Atypical angina	4	8
Dyspnea	2	4
Miscellaneous	2	4
Asymptomatic	5	10
Clinical Diagnosis		
Known CAD	42	78
Valve disease	5	10
IHSS	1	2
Arrhythmia	1	2
No disease	5	10

CAD = coronary artery disease; IHSS = idiopathic hypertrophic subaortic stenosis

TABLE 3.—*Electrocardiographic (ECG) Findings at Rest Before Exercise in 54 Patients With Ventricular Tachycardia or Ventricular Fibrillation*

Resting ECG Data	Patients Number	Patients Percent
Normal ECG	28	56
Prior MI	14	26
Left axis deviation	9	19
Left ventricular hypertrophy	5	10
Atrial fibrillation	3	6
Ventricular premature beats	4	8
Prolonged $QT_c \geq 0.44$ s	14	39

MI = myocardial infarction; QT_c = QT corrected for heart rate

focal beats. This arrhythmia occurred in 13 patients, 10 of whom had coronary artery disease. One patient had idiopathic hypertrophic subaortic stenosis and one had cardiomyopathy with ventricular arrhythmias. In all but one patient, spontaneous reversion to sinus rhythm occurred. One patient was converted to sinus rhythm by an intravenous infusion of lidocaine. The mean number of beats in the other 12 patients was 9 (range 4 to 14) and the mean heart rate during tachycardia was 167 beats per minute (range 120 to 280).

Ventricular fibrillation occurred in six additional patients. In each instance the arrhythmia began as a series of rapid depolarizations of a similar waveform, consistent with ventricular flutter (Figure 4). In one patient the rhythm deteriorated to a fine, irregular, rapid waveform, consistent with the usual type of ventricular fibrillation. This patient and two others required cardioversion. In each instance a single 400 watt-second DC shock was sufficient to restore a persistent sinus rhythm. In the other three patients ventricular fibrillation reverted spontaneously to sinus rhythm at 3, 7 and 14 seconds after the onset. The initial rates of ventricular fibrillation were 250, 280, 300, 315, 375 and 400 beats per minute. Clinical features of this group of 19 patients are summarized in Table 5.

Of the 19 patients who exhibited either unifocal ventricular tachycardia or fibrillation, 7 patients (38%) died over a mean follow-up period of 48 months (range 12 to 72 months). All deaths were of cardiac origin.

Multifocal ventricular tachycardia of four or more consecutive beats was less common than unifocal tachycardia of four or more beats and was observed in only five patients, three of whom had coronary artery disease. None of these patients died during the four-year follow-up period.

TABLE 4.—*Characterization of Ventricular Tachycardia (VT) and Ventricular Fibrillation in 54 Patients With and Without Known Coronary Artery Disease (CAD)*

Clinical Features	*Known CAD N = 42 (Percent)*	*No Known CAD N = 12 (Percent)*	P
Heart rate before VT	126 ± 19*	111 ± 22*	<.03
R-R′ interval†	0.36 ± 0.09*	0.44 ± 0.11*	<.05
Ischemic ST depression	28/42 (66)	2/12 (17)	<.01
Preceding VPBs	36/42 (85)	4/8 (50)	<.05
Chest pain	32/42 (76)	1/12 (10)	<.01
VT Onset			
During exercise	38/42 (76)	10/12 (83)	NS
After exercise	22/42 (53)	4/12 (33)	NS
Unifocal VT	30/42 (71)	8/12 (67)	NS
Multifocal	13/42 (31)	4/12 (33)	NS
Unifocal VT ≥ 4 beats	10/42 (24)	3/12 (25)	NS

CAD = coronary artery disease, NS = not significant, VPBs = ventricular premature beats

* ± 1 standard deviation.
†See text for definition.

TABLE 5.—*Characteristics of 19 Patients With Unifocal Ventricular Tachycardia (≥ 4 Beats) or Ventricular Fibrillation**

Patient Characteristics *Age Mean 54.5 yr (range 48 to 84)*	*Number/Number*	*Percent*
Positive treadmill test	15/19	79
Abnormal LV function	9/15	79
Ejection fraction mean, % (range 34% to 76%)	52.8	
Left main CAD	4/15	26.5
3-Vessel disease	7/15	46.5
2-Vessel disease	6/15	40
No CAD	2	13
Mortality, yr†	4	38

CAD = coronary artery disease; LV = left ventricular

*Only 15 patients had coronary arteriography.
†Complete follow-up data were not obtainable.

Discussion

The present study has several limitations. Because it was a retrospective analysis, some episodes of ventricular tachycardia of short duration may not have been identified and its actual incidence may have been underestimated. The diagnosis of cardiac disease was based on clinical data only and coronary arteriography was not done on all the patients. It is possible that some of the noncardiac patients actually had coronary artery disease.

The clinical diagnosis in the subgroup of patients with coronary artery disease was probably reasonably accurate, however, because 25 of these patients had arteriography, and coronary artery disease was present in all. Most had positive exercise tests. Complete follow-up data were available only in patients who had ventricular tachycardia of four or more unifocal beats or ventricular fibrillation. In the remaining patients, we were unable to obtain complete follow-up data regarding survival. The purpose of this study, however, was not primarily to examine the prognosis of exercise-induced ventricular tachycardia of short duration—that is, four consecutive beats or less.

Previous publications regarding exercise-induced ventricular arrhythmias have not been confined to studies of ventricular tachycardia or fibrillation, as these arrhythmias are rare.[3(p151)-5] In a previous study in this hospital of patients with stable angina and significant coronary artery disease as seen by arteriography, the incidence of exercise-induced ventricular tachycardia was 5% (5/102). No episodes of ventricular fibrillation were noted.[6] This incidence is slightly higher than the 4% reported in this study, but clearly there were differences in the two patient populations. McHenry and coworkers reported a 3% incidence of ventricular tachycardia in 197 patients with angiographically proved coronary artery disease.[5] These reports attest to the safety of exercise tests even in patients with coronary artery disease because the incidence of ventricular tachycardia and ventricular fibrillation is low and, in the present study, only three patients required cardioversion and no serious complications followed the arrhythmia.

Mokotoff and associates carried out a similar analysis of 26 patients with ventricular tachycardia associated with exercise testing[7]: 16 (70%) had coronary artery disease and 8 had no evidence of heart disease. Ambulatory monitoring following the test showed ventricular tachycardia in 19% (5/26) of patients and malignant ectopy in 54% (14/26). Thus, exercise-induced ventricular tachycardia correctly predicted the presence of serious ventricular arrhythmias during ambulatory monitoring in 73% of patients. No episodes of ventricular fibrillation were reported. During a mean follow-up period of 21 months, in 24 patients only one death occurred. Because this study was based on a selected group of patients, it was not possible to determine the incidence of ventricular

tachycardia in the population data base. Similar data were presented by Codini and colleagues, who described 47 patients with exercise-induced ventricular tachycardia.[8] The incidence was 0.08% in 5,730 treadmill tests compared with the incidence in our study of 0.02% in 2,565 patients. Other features of the patients were similar to ours. Exertional hypotension was common in the patients seen by Codini and coworkers but was observed in only one of our patients.

Our results are in general agreement with those of the above studies in regard to the high prevalence of coronary artery disease in patients with ventricular tachycardia and the general characteristics of the arrhythmia. The mortality of patients with unifocal ventricular tachycardia of four beats or more and ventricular fibrillation is considerably higher in our study than in that reported by Mokotoff and associates—that is, a 4-year mortality of 38% versus a 21-month mortality of 4%—but the populations studied are probably different.[7] It is difficult to determine if the occurrence of ventricular tachycardia or fibrillation is a marker for a higher mortality than in patients with a similar degree of coronary artery disease and left ventricular dysfunction who did not have exercise-induced tachycardia or fibrillation. As can be seen in Table 4, most of the patients in the present study had multivessel coronary artery disease and abnormal left ventricular function, and these factors above are associated with a four-year mortality of between 20% and 30%.[10] The occurrence of ventricular tachycardia or fibrillation during exercise thus appears to be associated with a higher mortality, but this cannot be determined accurately from the present study.

Woelfel and co-workers recently described the cases of 14 patients with exercise-induced tachycardia of 5 beats or more in duration in whom β-blockade suppressed the arrhythmia in repeat exercise studies in 79% (11/14). Only six of their patients had coronary artery disease and six had no evidence of heart disease.[10] These results are encouraging, and this method of treatment deserves consideration in patients with coronary artery disease. Similar good results were reported for verapamil.[11]

In summary, the present study indicates that the incidence of ventricular tachycardia during diagnostic exercise testing in patients without coronary artery disease is less than 1%. In patients with the disease, the incidence is approximately 4% and ventricular fibrillation occurs in about 1%. Most episodes of ventricular tachycardia are nonsustained multifocal or unifocal runs of four or fewer consecutive beats. A subgroup of 13/48 patients was identified with unifocal tachycardia of four consecutive beats or more. In this group of patients and in six patients with ventricular fibrillation, the four-year cardiac mortality was 38%. This is a higher mortality than the 20% to 30% four-year mortality that has been observed in the average patient with stable angina, angiographically shown multivessel disease and abnormal left ventricular function.[10] The appearance of sustained ventricular arrhythmias is not diagnostic of coronary artery disease since in this study population there was a higher prevalence of the disease compared with other forms of heart disease.

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Prevalence of HTLV-III Antibody Among New Mexico Residents With Hemophilia

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Persons with hemophilia who have received therapy since 1978 are at risk for the acquired immunodeficiency syndrome. Plasma and serum specimens collected from 1980 to 1985 from 73 New Mexico residents with hemophilia were tested by enzyme immunoassay for antibody to human T-cell lymphotropic virus type III (HTLV-III), and positive results were confirmed by Western blot. Antibody to HTLV-III was first detected in New Mexico residents with hemophilia in 1981. Among 49 persons tested in 1984-1985, seropositivity was found in 35%. Of these, 17 of 32 (53%) commercial concentrate versus 0 of 17 cryoprecipitate users were seropositive (P = .002). Of the 7 with hemophilia B, 3 (43%) were seropositive versus 14 of 42 (33%) with hemophilia A. Of 17 Albuquerque residents with hemophilia, 2 (12%) were seropositive as compared with 15 of 32 (47%) persons with hemophilia who resided outside the city (P = .02).

Compared with patients with hemophilia outside of Albuquerque, those living in Albuquerque tended to have milder disease and to use cryoprecipitate rather than commercial concentrate. Less frequent treatment (mild disease) and use of cryoprecipitate were associated with a decreased risk of HTLV-III infection.

(Waskin H, Smith KJ, Simon TL, et al: Prevalence of HTLV-III antibody among New Mexico residents with hemophilia. West J Med 1986 Oct; 145:477-480)

Hemophilia-associated acquired immunodeficiency syndrome (AIDS) is a disease of major concern to those who must receive factor replacement therapy. As of April 1986, the Centers for Disease Control have reported 170 cases of hemophilia-associated AIDS in the United States. It is estimated that in the United States there are 12,000 to 13,000 persons with hemophilia who are at risk for infection with the human T-cell lymphotropic virus type III (HTLV-III),* the causative agent of AIDS.[1]

The prevalence of antibody to HTLV-III in hemophiliac patients transfused with factor concentrate has varied among geographic locations surveyed, from 34% in the United Kingdom[2] to 74% in California.[3] Before the availability of heat-treated factor VIII or IX concentrates, persons who received only cryoprecipitate were felt to be at lower risk of exposure to virus when compared with those who received commercially produced concentrate. However, 40% of patients receiving only cryoprecipitate were found to be seropositive in 1984 in a survey in Seattle.[4]

In this study we investigated the prevalence of antibody in New Mexico residents with hemophilia to define the risk from commercial concentrate as compared with the risk from cryoprecipitate produced locally. New Mexico is estimated to have 75 persons with hemophilia who require replacement therapy, most of whom participate in a statewide hemophilia program.

Patients and Methods

Study Population

The study population consisted of 73 men with hemophilia residing in New Mexico who had required factor VIII or IX replacement since 1978 and were seen annually in the statewide hemophilia program. Clinical data obtained included a

*Human immunodeficiency virus, or HIV, has been recently proposed as a more simplified name by The Human Retrovirus Subcommittee of the International Committee on the Taxonomy of Viruses, reported in *Science* (1986; 232:697).

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ABBREVIATIONS USED IN TEXT
AIDS = acquired immunodeficiency syndrome
HTLV-III = human T-cell lymphotropic virus type III

medical history, the number of bleeding episodes in the previous year, the type and amount of replacement therapy used and a physical examination. Laboratory data included a complete blood count, platelet count, total lymphocyte count and serum aspartate aminotransferase (glutamic-oxaloacetic transaminase), alanine aminotransferase (glutamic-pyruvic transaminase) and alkaline phosphatase levels and hepatitis B surface antigen. Serum and plasma specimens were stored at −20°C or −80°C.

A person was classified as a cryoprecipitate user if this was the sole replacement product (apart from packed cells or plasma) used since 1978. If he had ever used commercial factor concentrate since 1978, he was classified as a commercial product user. Factor activity was used to classify hemophilia as mild (greater than 5% activity), moderate (1% to 5% activity) or severe (less than 1% activity).

Replacement Therapy

The cryoprecipitate used was prepared solely from volunteer donations at the regional blood center in Albuquerque.[5] For the average bleeding episode, replacement therapy would necessitate 1,000 to 1,500 units of factor VIII, exposing a person to blood from 10 to 15 donors. Commercial factor VIII or IX concentrate (Highland Therapeutics, Division of Baxter-Travenol, Glendale, California; Cutter Laboratories, Berkeley, California; Alpha Therapeutics, Los Angeles, or Armour Pharmaceutical Company, Kankakee, Illinois) was supplied to a patient as a lyophilized product and was reconstituted for home usage by the patient or a family member. One vial of commercial concentrate represented blood product from several thousand donors throughout the United States, depending on the manufacturer's procedures. Since January 1985, heat-treated commercial products from the same sources have been distributed because heat treatment at 56°C has been shown to inactivate HTLV-III in vitro.[6]

Serologic Testing

The HTLV-III immunoglobulin G antibody assay was done on all specimens using the Abbott enzyme-linked immunosorbent assay. A test was considered positive if the optical density ratio of specimen to control at 490 nm was 3.0 or greater on repeat testing. Positive tests were confirmed by Western blot analysis.

Statistical Methods

Data were analyzed by the Mann-Whitney rank sum test, Fisher's exact test and the Student's *t* test. All tests were two-tailed unless otherwise stated.

Results

When serum specimens collected in 12-month periods from June 1980 to May 1985 were tested for the presence of HTLV-III antibody, none from 1980-1981 were seropositive, whereas 2 of 39 (5%) from 1981-1982 and 14 of 42 (33%) from 1984-1985 showed serologic evidence of HTLV-III infection (Figure 1). Among 49 persons with hemophilia who had at least one specimen available from January 1984 through May 1985, 3 of 7 (43%) requiring factor IX as compared with 14 of 42 (33%) of those requiring factor VIII were seropositive (not significant). Among the 49, severe hemophilia, commercial concentrate use and residence outside of Albuquerque all increased the risk of HTLV-III infection.

Seropositive patients were significantly more likely to be treated more than 12 times per year and were twice as likely to have a history of spontaneous bleeding as compared with those who were seronegative ($P \leq .02$ for each comparison, Table 1). Seropositive recipients also tended to be older, to have been treated longer and to be more likely to have a history of a major operation or major bleeding episodes, but these comparisons were not statistically significant (Table 1).

Of 32 commercial concentrate users, 17 (53%) were seropositive compared with 0 of 17 patients with hemophilia who had used cryoprecipitate only ($P = .002$). Hemophilia was severe in 1 of 17 (6%) cryoprecipitate as compared with 19 of 32 (59%) commercial concentrate recipients, mild in 12 of 17 (71%) cryoprecipitate versus 2 of 32 (6%) commercial concentrate recipients, and treatment 12 times per year or more was required in 2 of 17 (12%) cryoprecipitate versus 21 of 32 (66%) commercial concentrate recipients ($P < .001$ for each comparison).

Seropositive persons with hemophilia received a median

TABLE 1.—*Presence or Absence of Antibody to Human T-Cell Lymphotropic Virus Type III (HTLV-III)*

Clinical Characteristics	HTLV-III Antibody		Significance, P
	Positive	Negative	
Patients, number	17	32	
Median number of units used per annum	34,500	6,660	<.001
Treatment required >12 times/yr, percent	71	34	.02
History of spontaneous bleeding, percent	88	44	.002
History of major operation or bleeding episodes, percent	71	56	NS
Median treatment years	16.0	11.5	NS
Median age, yr	21.5	16.5	NS

NS = no significance

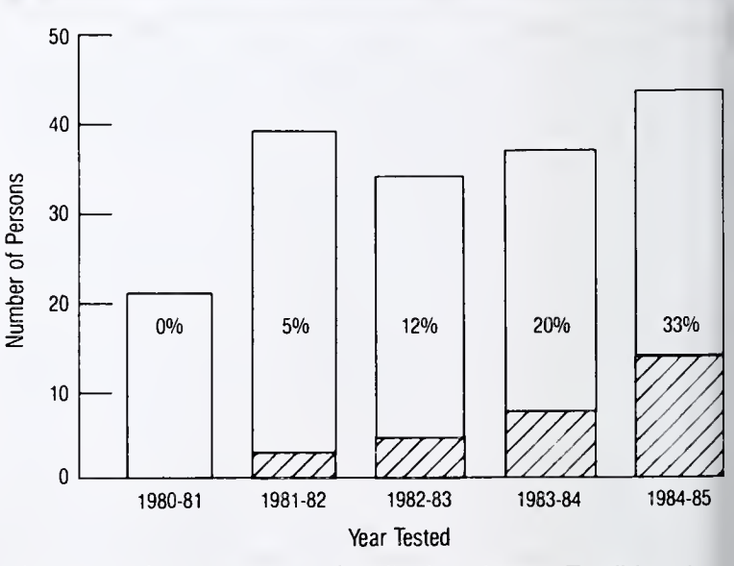

Figure 1.—Seroprevalence of antibody to human T-cell lymphotropic virus type III from 1980 to 1985 in New Mexico residents with hemophilia (given in 12-month intervals, June through May).

of 34,500 units per year compared with 6,600 units per year among seronegative persons with hemophilia ($P < .001$, Table 1). Among those who were seronegative, commercial concentrate users received a greater median number of units per year (25,170) compared with those who received cryoprecipitate only (3,600 units per year, $P < .01$). Among commercial concentrate users, the difference in the median number of units per year used by seropositive patients with hemophilia (34,500) versus those who were seronegative (25,170) was not statistically significant. All 17 seropositive patients with hemophilia, however, used commercial concentrate alone, whereas 4 of 15 seronegative "commercial concentrate" users were predominantly cryoprecipitate users who used commercial concentrate only while traveling. If only commercial concentrate use is included in the analysis, the 17 seropositive patients with hemophilia received a median of 34,500 units per year as compared with 8,500 units per year among the 15 seronegative commercial concentrate users ($P < .05$).

Unexpectedly, only 2 of 17 (12%) Albuquerque residents with hemophilia as compared with 15 of 32 (47%) patients with hemophilia outside of Albuquerque were seropositive ($P < .001$, Table 2). Compared with those outside of Albuquerque, Albuquerque residents with hemophilia were significantly more likely to have mild hemophilia and to use cryoprecipitate rather than commercial concentrate (Table 2).

The median total lymphocyte count, median platelet count, mean hemoglobin and percentage of patients with abnormal aminotransferase levels did not differ between seropositive or seronegative groups. Of 29 seronegative patients, 4 had hepatitis B antigenemia as compared with 1 of 17 seropositive patients (not significant). There was no association of seroconversion with lymphadenopathy, splenomegaly or hepatomegaly. AIDS did not develop in any patients, but two had idiopathic thrombocytopenic purpura.

TABLE 2.—*Comparison of New Mexico Residents With Hemophilia Who Resided in Albuquerque Versus Elsewhere in the State**

Patient Characteristics	Albuquerque Resident	Albuquerque Nonresident	Significance, P
Seroprevalence of HTLV-III	12 (2/17)	47 (15/32)	<.001
Cryoprecipitate users with hemophilia A	67 (10/15)	26 (7/27)	<.01
Those with mild hemophilia	59 (10/17)	13 (4/32)	<.001

HTLV-III = human T-cell lymphotropic virus type III

*Values given in percent, with numbers in parentheses indicating numbers of patients.

Discussion

Despite a steady increase in the proportion of New Mexico residents with hemophilia infected with HTLV-III, the proportion (35%) who were found to be infected in 1984-1985 is significantly lower than rates of 50% to 74% reported among persons with hemophilia in other states during the same period (Table 3).[3,4,7-12] The significantly lower seroprevalence among residents of Albuquerque with hemophilia as compared with those living elsewhere in the state appears to be due to increased availability of cryoprecipitate and a decreased likelihood that persons with mild hemophilia living outside of Albuquerque would participate in the regional hemophilia program in Albuquerque.

One explanation for the lower seropositivity in persons in New Mexico with hemophilia as compared with those reported in other states is that a higher proportion of patients have been on a maintenance regimen of only locally produced cryoprecipitate since 1978 (Table 3). Cryoprecipitate users make up 35% (17 of 49) of persons with hemophilia in this study as compared with 30% (14/46) in San Francisco, 21% (22/103) in Hershey, Pennsylvania, 21% (6/29) in Cleveland and 37% (15/41) in Seattle. Regardless of the source of the cryoprecipitate, cryoprecipitate users are exposed to fewer donors as compared with commercial concentrate users. For a patient with hemophilia who requires 1,500 units of factor an average of 12 times a year, the cryoprecipitate user would be exposed to plasma of about 180 donors a year as compared with 10,000 or more donors if their maintenance regimen was commercial concentrate.

In addition, cryoprecipitate produced in New Mexico may have been less likely to be infected with HTLV-III as compared with cryoprecipitate prepared in areas with higher rates of HTLV-III infection. It was of interest that none of 17 New Mexico cryoprecipitate users were seropositive as compared with a seroprevalence of 14% and 40% among cryoprecipitate users in San Francisco and Seattle, respectively (Table 3).[4,8] In a survey of 166 gay and bisexual men in Albuquerque and Santa Fe in 1985, 20% were found to have antibody to HTLV-III.[13] Presumably the prevalence of infection among

TABLE 3.—*Geographic Variability Among Seroprevalence of Antibody to Human T-Cell Lymphotropic Virus Type III in Persons With Hemophilia**

Location of Research Center	Year Specimens Drawn	Overall Prevalence	Prevalence by Blood Product: Commercial Factor VIII	Prevalence by Blood Product: Commercial Factor IX	Prevalence by Blood Product: Cryoprecipitate
Albuquerque	1984-1985	35 (17/49)	56 (14/25)	43 (3/7)	0 (0/17)
Georgia[9]	1984	72 (18/25)	78 (18/23)	0 (0/2)	ND
Kansas City-Pittsburgh[11]	1984†	61 (49/80)	74 (61/82)	30 (9/30)	15 (9/59)
San Francisco[8]	1984	74 (34/46)	100 (28/28)	100 (4/4)	14 (2/14)
Hershey, Penn[12]	1982-1984	50 (51/103)	74 (51/69)	0 (0/12)	0 (0/22)
Cleveland[10]	1984	62 (18/29)	78 (18/23)	ND	0 (0/6)
Seattle[4]	1984	63 (26/41)	ND	ND	40 (6/15)

ND = no data

*Values given in percent, with numbers in parentheses indicating number positive versus number with hemophilia.
†Overall prevalence refers to 1984; prevalence by commercial and local products refers to 1982-1984.

gay and bisexual men in New Mexico was even lower before the self-deferral policy for high-risk donors was implemented in 1983.

It was also of interest that the prevalence of HTLV-III antibody in commercial factor VIII users in New Mexico was 56%, whereas other centers have reported a seroprevalence of 74% to 100% in commercial concentrate recipients. Because New Mexico residents with hemophilia used the same commercial sources as persons with hemophilia in other centers, the source of commercial concentrates cannot account for the observed differences in seroprevalence. Similarly, because currently available testing procedures are both sensitive and specific when applied to those in high-risk groups, differences in seroprevalence should not be influenced by differences in testing procedures.[14]

In comparison with commercial concentrate recipients described in other studies, our population appeared to be more likely to have mild hemophilia, to be younger and to require fewer units of factor replacement a year. For example, among seropositive patients with hemophilia, the median number of units used per annum was 111,101 in the Georgia study as compared with 34,500 in our study.[9] In addition, because the number of units given to a person with hemophilia is determined by body weight, younger hemophiliac patients tend to be exposed to fewer donors. As such, it was of interest that the median age of factor VIII recipients in New Mexico was 18, whereas the median age in the Georgia study was 27.

The preceding discussion illustrates some of the limitations in comparing or extrapolating seroprevalence data between research centers. Differences in the characteristics of the study population, particularly age or severity of hemophilia and access to local cryoprecipitate, are important factors in determining the risk of exposure to contaminated blood products.

Although our findings suggest that locally produced cryoprecipitate is associated with a very low risk of transmitting HTLV-III infection, the screening of blood donors for HTLV-III antibody implemented since March 1985 should further decrease this risk. In addition, since January 1985, patients receiving commercial concentrate have received only a heat-treated product. Heat treatment has been shown to inactivate the virus and to decrease infectivity in vitro, and studies in animals suggest that the risk of hepatitis transmission may be reduced by heat treating at 60°C for 10 hours.[6,15] As such, randomized studies comparing the risk of HTLV-III infection as well as hepatitis B, non-A, non-B hepatitis and δ-hepatitis among recipients of cryoprecipitate and heat-treated concentrate may be appropriate.

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Sclerotherapy for Bleeding Esophageal Varices After Randomized Trials

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Endoscopic sclerotherapy remains an uncertain therapy for bleeding esophageal varices. Several recently reported randomized trials address the efficacy of immediate, long-term and prophylactic sclerotherapy. Analysis of these studies suggests that sclerotherapy may stop acute bleeding but has little impact on survival of an acute bleeding episode. Ongoing sclerosis reduces the incidence of rebleeding episodes and improves survival for those patients fortunate enough to survive the acute bleeding episode. Prophylactic therapy is an exciting concept limited by difficulty in identifying "high-risk" patients and by the high rate of complications associated with sclerotherapy.

(Lieberman DA: Sclerotherapy for bleeding esophageal varices after randomized trials. West J Med 1986 Oct; 145:481-484)

Endoscopic sclerotherapy is now a popular, albeit uncertain, therapy for bleeding esophageal varices. The resurgence of interest in endoscopic sclerotherapy must be astounding to students of medical history who observed the apparent demise of this procedure in the 1950s. During the past seven years, hundreds of papers on this subject have been published—primarily in the form of case series and anecdotal reports. Now, reports of randomized clinical trials assessing the efficacy of sclerotherapy are finally emerging.

In this article I critically examine the randomized trials involving sclerotherapy to determine if any consensus can be established on several outstanding issues. First, does sclerotherapy have any impact on early survival after a variceal hemorrhage? Second, does ongoing sclerotherapy prevent rebleeding and improve long-term survival compared with other forms of treatment? Third, does prophylactic sclerotherapy for nonbleeding varices prevent rebleeding and improve survival?

The complexities of evaluating treatment of bleeding varices have been previously elucidated.[1,2] Several key variables must be considered before reviewing the available clinical trials. The composition of patients in a study may greatly influence the outcome data. The hepatic reserve reflected in part by the Child classification remains a prognostic factor of great significance.[3] Survival and rebleeding are closely related to Child's class, irrespective of the form of treatment.[3,4] Therefore, the different distributions of Child's classes among studies may affect outcome data. The cause of the underlying liver disease may also affect outcome. Patients with alcoholism who stop drinking may fare better than patients with irreversible nonalcoholic liver diseases, irrespective of treatment.[3] If they continue to drink, rebleeding and death are more common.[5] The studies selected for review have a predominance of patients with alcoholism (52% to 84%). Controlled trials from Egypt[6,7] are not included here because the most common cause of liver disease was schistosomiasis, which appears to have a better response to sclerotherapy than other liver diseases. The timing of entry into the study has been shown to influence survival data.[2] Early mortality from variceal hemorrhage is quite high regardless of treatment. The beneficial long-term effects of a particular treatment may be obscured by high early mortality. This may be especially crucial for sclerotherapy, which would not be expected to have maximal benefit until the varices are obliterated—a process requiring weeks to months. Therefore, it is probably quite legitimate to separate the early and late phases of treatment to determine if a particular form of treatment (such as sclerotherapy) is beneficial during either period.

Of secondary importance in evaluating the available clinical trials are differences in sclerotherapy technique—differences that are, quite literally, oceans apart. The uses of rigid versus flexible endoscopes, sclerosants (morrhuate sodium and sodium tetradecyl sulfate in the United States; Polidocanol in Europe) and intravariceal versus paravariceal injections remains unsettled and complicates any comparisons between the studies. Hence, American readers must be cautious about extrapolating European results to the American experience. Finally, the volume of sclerosant used in each injection and the cumulative amount per session remain items of controversy and differ in various studies.

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Sclerotherapy for Acute Variceal Bleeding

Four controlled trials[8-11] have compared sclerotherapy with balloon tamponade for control of bleeding varices. The impetus for such trials was case series reporting greater than 90% success in stopping acute variceal bleeding with sclerotherapy.[12,13] The results suggest that sclerotherapy is an effective means for the initial control of hemorrhage but that rebleeding is common and early mortality is not influenced by sclerotherapy (Table 1). Studies from Copenhagen and Sweden showed no differences between sclerotherapy and control treatment in rebleeding and survival during the first 40 days of treatment.[8,9] In the smaller study by Paquet and Feussner, primary control of acute bleeding was achieved in 95% of sclerotherapy patients and 73% of patients managed with balloon tamponade.[10] Nevertheless, early rebleeding and survival were similar in the medical and sclerotherapy groups. The first American study to prospectively examine sclerotherapy for acute bleeding in a controlled trial[11] found a significant reduction in early rebleeding among sclerotherapy patients compared with controls. This benefit, however, appeared to be limited to patients who had spontaneously stopped bleeding before sclerotherapy. Rebleeding rates were similar in sclerotherapy and control patients who were actively bleeding at the time of endoscopy.

Sclerotherapy for acute bleeding was compared with emergent surgical treatment in a study by Cello and co-workers[14] limited to patients most likely to die of variceal hemorrhage (Child's class C). Survival in both groups was dismal, with only 42% of all patients alive 30 days after the index hemorrhage. These five studies suggest that although bleeding may be controlled for the short term by sclerotherapy, early rebleeding is common and early mortality remains high.

Ongoing Sclerotherapy

The ability of sclerotherapy to prevent recurrent bleeding and improve long-term survival has been examined in five studies (Table 2).[4,8,9,15,16] Three of these studies suggest that long-term survival is improved by sclerotherapy when it is compared with no therapy at all. In one study that failed to show improvement,[15] all patients received some sclerotherapy, but in only half of the population was an attempt made to obliterate the varices. Thus, both groups received sclerotherapy and, not surprisingly, had similar survival results. The timing of randomization may have influenced the outcome of the study by Westaby and associates.[4] Significant improvement in survival was observed with sclerotherapy, but 34 of 150 patients (23%) were excluded because of early

TABLE 1.—*Sclerotherapy for Acute Bleeding Episode—Randomized Trials*

Study	Group*	N	Early Rebleeding: Patients, Number	Early Rebleeding: Bleeding Episodes, Number	Short-term Survival: 0-40 d, Percent	Short-term Survival: 180 d, Percent
Copenhagen, 1984[8]	S	93	34	40	52 (NS)	
	C	94	28	37	55	
Paquet and Feussner, 1985[10]	S	21	4	...	90 (NS)	86 ($P<.01$)
	C	22	7	...	73	50
Söderlund and Ihre, 1985[9]	S	57	16	19	72 (NS)	
	C	50	16	31	64	
Larson et al, 1986[11]	S	44	10 ($P<.01$)	15 ($P<.02$)	95 (NS; 0-14 d)	
	C	38	20	32	87	

NS = no significance

*S = sclerotherapy, C = control

TABLE 2.—*Sclerotherapy Versus Control—Long-term Results*

Study and Yrs of Follow-up	Group*	N	Recurrent Bleeding Episodes: Patients, Number	Recurrent Bleeding Episodes: Bleeds, Number	Recurrent Bleeding Episodes: Bleed/Pt/Mo	Survival, Percent
Terblanche et al, 1983,[15] 5 yrs	S	37	14	43 ($P<.01$)	...	38 (NS)
	C	38†	20	73	...	37
Copenhagen, 1984,[8] 2 yrs	S	93	45	64 (NS)	...	36 (NS)
	C	94	51	138	...	25
Early survivors‡	S	48	15	24 ($P<.01$)	...	72 ($P<.03$)
	C	52	31	101	...	50
Westaby et al, 1985,[4] 3 yrs	S	56	31	66 ($P<.01$)	...	68 ($P<.01$)
	C	60	49	125	...	47
Korula et al, 1985,[16] 1-2 yrs	S	63	...	...	0.2 ($P<.01$)	50§ ($P<.05$)
	C	57	...	...	0.8	40
Söderlund and Ihre, 1985,[9] 1 yr	S	57	32	50	0.05 ($P<.001$)	53 (NS)
	C	50	33	99	0.16	42

NS = no significance

*S = sclerotherapy, C = control
†Controls received emergency sclerotherapy.
‡Analysis of subpopulation who survived the first 40 days after acute hemorrhage.
§Excluding patients referred for shunt operation.

death. The Copenhagen study also supports the notion that if patients can survive the initial bleeding episode, sclerotherapy may enhance long-term survival.[8] When patients alive 40 days after the index bleeding episode were analyzed as a separate group, both rebleeding rates and mortality were improved significantly by sclerotherapy (Table 2). Söderlund and Ihre[9] also noted a reduction in rebleeding among sclerotherapy patients, particularly after varices had been completely obliterated. Although long-term survival was similar in both sclerotherapy and control groups, the incidence of death due to bleeding varices was significantly reduced in sclerotherapy patients. This reduction in mortality due to variceal hemorrhage is a common theme in all of these reports and is reinforced by the only American study available.[16] Korula and associates[16] found that bleeding as a cause of death was much more common among controls (25%) than among sclerotherapy patients (11%). The high rate of patient dropout (17% to surgical treatment and 21% lost to follow-up) may have influenced the outcome of this study.

In summary, these studies suggest that the risk of rebleeding and death is reduced by ongoing sclerotherapy when compared with no therapy. It also appears that rebleeding is reduced after sclerotherapy when compared with medical treatment with metoprolol.[17] Recurrence of varices after obliteration was common in these studies (more than 60%), suggesting the need for follow-up sclerotherapy sessions to maintain this benefit.

Emergent and Long-term Sclerotherapy—Summary

The reality of emergent sclerotherapy is something less than the hopes promulgated by early case series. We can effectively stop acute variceal hemorrhage (albeit briefly), which may provide the time needed to institute more definitive long-term therapy. Nevertheless, rebleeding is common and mortality approaches 30%[13] during the first 30 days after variceal hemorrhage. The failure of sclerotherapy to prevent rebleeding and death during the initial one to two months is probably due to incomplete obliteration of the varices. Ongoing sclerotherapy does seem to be effective at reducing bleeding and improving survival in Europe, but only after patients survive the initial bleeding period. Most rebleeding in the long-term sclerotherapy treatment groups occurs during the first month before complete variceal obliteration. One point comes through clearly from the studies of emergent and long-term sclerotherapy: as long as the varices persist, the risk of bleeding remains high. Studies under way in the United States will attempt to reproduce these results with "American" techniques. These data further suggest that the major benefit of sclerotherapy comes after a patient has managed to survive an acute bleeding episode. This is a sobering conclusion after years of promising case series and has focused attention on treatment that can affect early survival.

Prophylaxis

If early mortality from variceal bleeding is high,[2] especially in patients with poor hepatic reserve or alcohol abuse, perhaps prevention of the index bleeding episode may improve long-term survival in these patients. About one in three persons with cirrhosis with varices will have a variceal bleed, and, thus far, there are no reliable criteria to identify this high-risk group. Endoscopic findings such as large varices[18] or evidence of submucosal bleeding are potential harbingers of variceal hemorrhage. Prospective studies are still needed to identify specific factors that increase the likelihood of bleeding from varices. Patients with poor hepatic reserve (Child's class C) are more likely to die of the first bleeding episode. Hence, for lack of better data, these patients constitute a possibly "high risk" group. Paquet identified such patients and randomly assigned them to treatment with sclerotherapy or no treatment before the first hemorrhage.[19] During three years of follow-up, 29 of 33 control patients bled from varices and 21 (64%) died. Only 3 of 32 sclerotherapy patients bled from varices and this group had 6 deaths (19%).

Witzel and co-workers[20] evaluated prophylactic sclerotherapy in a randomized controlled trial in 109 patients with cirrhosis with various degrees of hepatic reserve and varices. Of the 109 patients, 81% were in Child's class A or B, and only 31% had "large" varices. During a two-year follow-up, the frequency of variceal bleeding and number of deaths were decreased in patients receiving sclerotherapy compared with controls, irrespective of the size of the varices.

These two studies offer considerable hope for prophylactic sclerotherapy. If confirmed in large clinical trials, this may be a reasonable approach in "high-risk" patients or perhaps all patients with known varices. It should be noted, however, that the prophylactic shunt operation was abandoned in the late 1960s because survival rates were not improved.

Complications

The benefits of sclerotherapy must be balanced against the risks. This is especially true when prophylactic sclerotherapy is entertained in a patient who has never bled from varices. The true incidence of complications may vary depending on the technique and sclerosant used. Galambos found a complication frequency of 41% in reported prospective studies.[1] It is estimated that 10% to 15% of patients will have a significant complication.[21] Esophageal ulceration, chest pain and fever occur in most patients following treatment. Serious complications of sclerotherapy are life-threatening hemorrhage,[22] esophageal perforation (3% to 4%) and stricture formation (5% to 6%). The prevalence of pleural effusion after sclerotherapy may approach 50%.[23] These effusions are exudative and may arise from inflammation of the mediastinal pleura. Adult respiratory distress syndrome is an unusual sequela of sclerotherapy. Transient bacteremia may also be common[24] although careful sterilization of equipment, including the water supply,[25] may reduce the incidence.

Conclusions

Tentative conclusions can be derived from these randomized trials. Sclerotherapy may effectively control variceal hemorrhage during an acute bleeding episode but early mortality remains high. Ongoing sclerotherapy may reduce rebleeding and improve survival provided that varices are obliterated and remain obliterated. It makes sense now to compare surgical treatment and ongoing sclerotherapy results in patients with varying degrees of hepatic reserve (Child's class A and B) to determine which therapy most successfully improves survival and which is more cost-effective. Perhaps the greatest impact on survival can be made by identifying high-risk patients and using sclerotherapy before the first bleeding

episode. The high rate of complications from sclerotherapy should temper enthusiasm for treating asymptomatic patients with varices until this approach is proved in large studies.

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Plague Masquerading as Gastrointestinal Illness

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In clinical descriptions of human plague, fever and tender lymphadenitis are emphasized and gastrointestinal manifestations are rarely mentioned. A review of 71 human plague cases showed that gastrointestinal symptoms occurred commonly (57%). Vomiting (39%) was the most frequent symptom, with nausea (34%), diarrhea (28%) and abdominal pain (17%) occurring less often. Physicians treating patients who reside in or have recently visited plague-endemic areas should include plague in the differential diagnosis in the presence of gastrointestinal symptoms and fever.

(Hull HF, Montes JM, Mann JM: Plague masquerading as gastrointestinal illness. West J Med 1986 Oct; 145:485-487)

Human plague cases classically present with fever and tender lymphadenitis. Although gastrointestinal symptoms are not prominently mentioned in discussions of the clinical manifestations of plague, we have recently seen a number of patients with laboratory-confirmed plague who had gastrointestinal symptoms as the predominant or sole clinical manifestation of their *Yersinia pestis* infection. Because of the unusual presentations of these cases, we will discuss three instructive cases as an aid to differential diagnosis. In addition, we have reviewed records of cases of plague originating in New Mexico for the five-year period 1980 to 1984 to determine the prevalence of gastrointestinal symptoms in plague.

Patients and Methods

The New Mexico Health and Environment Department (NMHED) records clinical and environmental information for every case of plague that originates in New Mexico. Reporting of cases is likely to be complete because only two laboratories do fluorescent antibody testing and only one laboratory does serum antibody tests for plague. Satisfactory clinical records included any of the following: a complete copy of the hospital chart, a hospital discharge summary, an extract of the hospital records prepared by NMHED personnel according to protocols in use at the time of the case investigation and a death record from the Office of the Medical Investigator. A case of plague was defined as a person who had a clinical illness consistent with *Y pestis* infection and who had one of the following: identification of *Y pestis* from culture material, bacteria seen on fluorescent antibody stain for *Y pestis* on nonviable clinical material, a fourfold difference between acute and convalescent passive hemagglutination (PHA) titers taken at least ten days apart or a single convalescent PHA titer of 1:16 or greater. A case of bubonic plague had a bubo or swollen, tender lymph node noted on physical examination. A case of septicemic plague had a blood culture positive for *Y pestis* but no adenopathy noted on physical examination. NMHED records were reviewed for all patients with plague with the onset of their illness between January 1, 1980, and December 31, 1984. Records were reviewed to determine the presence or absence of nausea, vomiting, diarrhea or abdominal pain and other relevant clinical information.

Statistical tests used were the χ^2 and Fisher's exact test for 2×2 tables.

Reports of Cases

Case 1

A 13-year-old boy became ill at 3 AM with fever, nausea, vomiting and diarrhea. He was seen that morning by a physician. On physical examination he had a temperature of 38.9°C (102°F) and no lymphadenitis. He was treated with prochlorperazine and released. At 5 PM the next day, the patient returned to his physician. Physical examination at that time showed a temperature of 40°C (104°F), right lower quadrant pain and tender right inguinal lymphadenitis. His leukocyte count was 25,900 per μl with 39% polymorphonuclear leukocytes (PMNs) and 39% band forms. Bacteria were noted on the peripheral blood smear. Liver function tests showed a serum aspartate aminotransferase (AST, formerly glutamic-oxaloacetic transaminase) level of 709, alkaline phosphatase level of 244 and a lactic dehydrogenase (LDH) level of greater than 1,846 units per liter. Despite treatment with a regimen of gentamicin sulfate and tetracycline given intravenously, the patient rapidly became delirious, went into shock and died. On postmortem examination, the bacteria noted in the peripheral smear were fluorescent antibody positive for *Y pestis*.

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ABBREVIATIONS USED IN TEXT

AST = aspartate aminotransferase
GI = gastrointestinal
LDH = lactic dehydrogenase
NMHED = New Mexico Health and Environment Department
PHA = passive hemagglutination
PMN = polymorphonuclear [leukocyte]

Case 2

A 61-year-old woman became ill with chills and myalgias. That night she had the onset of nausea, vomiting, diarrhea, abdominal cramping, fever and headache. The next afternoon she went to an emergency room with additional complaints of tiredness, weakness and myalgias. On taking the history, it was noted that a daughter had had diarrhea one week previously. On physical examination she had a temperature of 40.4 °C (104.7°F), hypoactive bowel sounds and diffuse, mild abdominal tenderness. A leukocyte count was 13,700 per μl with 56% PMNs and 33% band forms. Liver function tests showed an AST level of 18 units per liter and an alkaline phosphatase value of 84 units per liter. Cultures were done of blood and stool specimens. The patient was treated empirically with a regimen of gentamicin and cefazolin sodium and her condition improved slowly. An admission blood culture was positive for *Y pestis* on the second day in hospital.

Case 3

The patient, a 71-year-old woman, had fever, vomiting and right flank and hip pain. On physical examination she had a temperature of 38.2°C (100.8°F) and deep right flank and costovertebral angle tenderness. A leukocyte count was 17,100 per μl with 66% PMNs and 27% band forms. The AST level was 27, the LDH concentration 208 and alkaline phosphatase level 43 units per liter; a total bilirubin value was 0.5 mg per dl. Urinalysis showed 10 to 15 erythrocytes, few leukocytes and few bacteria per high powered field. She was admitted to hospital for further evaluation. Blood and urine cultures were done and she was treated with ampicillin given intravenously. On the second hospital day, a blood culture was growing a Gram-negative rod. An ultrasound examination showed cholelithiasis. A cholecystectomy was done and gentamicin added to the therapy. The patient recovered uneventfully. Twelve days after admission, the organism was identified as *Y pestis*.

Results

In all, 71 cases of human plague were recorded in New Mexico during the study period. Satisfactory records noting the presence or absence of gastrointestinal (GI) symptoms were available for 65 (92%) of these cases. Of the 65 cases, 47 (72%) were bubonic and 18 (28%) were septicemic. The frequency of gastrointestinal symptoms is shown in Table 1. Gastrointestinal symptoms were more common in septicemic cases than in bubonic cases. Only the increased frequency of abdominal pain, however, is statistically significant. Fever was usually the first symptom of illness. Abdominal pain, diarrhea and vomiting began on a mean of 1.2, 1.3 and 1.4 days after the onset of illness, respectively. There were no significant differences between cases with and without GI symptoms in regard to age, sex, race, case-fatality rate, month of onset, prevalence of secondary plague pneumonia or time of onset to first physician visit or admission to hospital.

Other associated constitutional symptoms were fever, chills, malaise and headache. Fever was universal and malaise was reported in 40% of all cases. Chills and headache were noted more frequently in cases with GI symptoms (60% and 54%, respectively) than in cases without GI symptoms (39% and 25%, respectively). Gastrointestinal symptoms preceded node pain in 7 of the 18 (39%) cases of bubonic plague with GI symptoms for whom time of onset was known. Analysis of physical signs at hospital admission showed there were no significant differences in temperature, pulse, respirations or systolic or diastolic blood pressure between cases with or without GI symptoms. None of the patients were noted to have hepatomegaly or splenomegaly. When compared with cases without gastrointestinal symptoms, cases with gastrointestinal symptoms had higher total leukocyte counts (16,700 versus 12,900 per μl), percent band forms (26% versus 18%) and total percentage PMNs plus PMN precursors (87% versus 79%) on differential leukocyte count. When a blood culture was done, *Y pestis* was found in the blood more often in patients with GI symptoms (28 of 33, 85%) than in patients without GI symptoms (17 of 24, 71%). Gastrointestinal symptoms occurred more often in bubonic cases with a positive blood culture (15 of 27, 56%) than in bubonic cases with a negative blood culture (5 of 11, 45%). An AST level was recorded for 28 cases. The mean AST concentration for 16 cases with GI symptoms was 115 units per liter, with a range of 12 to 709 units per liter. For the 12 cases without GI symptoms, the mean AST level was 40 units per liter with a range of 10 to 124. Elevated AST levels were found in 44% of cases with GI symptoms and 33% of cases without GI symptoms. Although suggestive, none of these differences in laboratory findings reached statistical significance.

Discussion

Plague is a rare bacterial zoonosis caused by *Yersinia pestis*, a Gram-negative bipolar staining bacillus. Plague is widely distributed in rodents throughout the American West, but two thirds of human cases in the United States have originated in New Mexico. The vast majority of human plague cases are bubonic, presenting with a swollen, tender lymph gland in the groin, armpit or neck. When a physician is alert for the disease, the diagnosis of bubonic plague is straightforward. Prompt and proper treatment then results in low fatality rates. A smaller percentage of plague patients have septi-

TABLE 1.—*Frequency of Symptoms in 65 Plague Cases in New Mexico, 1980-1984*

Symptom	Septicemic Cases, N = 18 Patients		Bubonic Cases, N = 47 Patients		Total Cases, N = 65 Patients	
	Number	Percent	Number	Percent	Number	Percent
Nausea	8	44	14	30	22	34
Vomiting	9	50	16	34	25	38
Diarrhea	7	39	11	23	18	28
Abdominal pain	7	39	4	9	11	17*
Any gastrointestinal symptom	13	72	24	51	37	57

*P = .007—Fisher's exact test.

cemic plague and present with fever and no bubo. Because of the nonspecific presentation of septicemic plague, the diagnosis can be quite difficult and the case-fatality rate is higher.

The illustrative cases described here had gastrointestinal symptoms that were unusually prominent. This study indicates, however, that GI symptomatology is quite common in plague, affecting more than half of the patients. Gastrointestinal symptoms previously described in plague include abdominal pain, nausea, vomiting and initial constipation followed by diarrhea.[1,2] The diarrhea material may be bloody and melenic stools have also been described. A series from the United States describes abdominal nausea or vomiting in 13 of 19 (68%) plague patients.[2] In one series of 500 patients from Vietnam, vomiting and diarrhea or abdominal pain (or all) were present in 7% of patients with buboes, 14% of patients with bubo and bacteremia and 20% of patients with septicemia (Nguyen NT, Nguyen DT: Clinical considerations and therapeutics on 500 confirmed plague patients in Cho-Quam Hospital, unpublished data, Aug 1970). Another series from Vietnam found that "more than 50%" of 88 plague patients presented with vomiting.[3] In an outbreak of plague in Nepal,[4] 12 (46%) and 18 (69%) of 26 patients had vomiting and diarrhea, respectively. The findings of these studies concur with our findings and suggest that gastrointestinal symptomatology is common in plague.

Gastrointestinal symptoms associated with plague are thought to be a general response of the body to serious illness and stress rather than resulting from a specific gastrointestinal pathologic process.[1] Vomiting and diarrhea are common symptoms of Gram-negative septicemia caused by organisms other than *Y pestis*. McCabe and Jackson noted nausea and vomiting in 43% and diarrhea in 21% of their patients with Gram-negative septicemia.[5] Diarrhea has also been described as occurring in patients with meningococcemia[6] and those with *Streptococcus pneumoniae* bacteremia.[7] Abdominal pain, such as described in case 3, might be caused by intra-abdominal buboes. Lymphadenopathy of mesenteric or retroperitoneal nodes has been found in patients with plague in both the presence and the absence of associated inguinal node involvement.[8-10] The frequency with which this occurs remains unknown, and the role of intra-abdominal buboes in causing abdominal pain remains speculative. An alternative explanation of abdominal pain in plague could be enlargement of the liver or spleen. Hepatosplenomegaly and liver dysfunction have been observed in cases of plague.[11,12] Although 44% of patients with GI symptoms in our study had an abnormal AST level, this was not substantially different from patients without GI symptoms. None of the patients in this study were noted to have hepatosplenomegaly.

Gastrointestinal symptoms occurred frequently in patients with confirmed plague in this study. The onset of GI symptoms occurred early in the course of the illness, sometimes preceding the appearance of lymphadenopathy or lymph node pain in bubonic plague. Additionally, GI symptoms occurred more frequently in septicemic plague, in which no bubo was present. Physicians who are treating patients who reside in or have recently traveled to plague-endemic areas should, therefore, not be reassured by the presence of symptoms suggesting that illness originates in the gastrointestinal tract. A careful history and physical examination of patients with GI symptomatology may yield important epidemiologic clues or reveal node pain or lymphadenopathy. A differential leukocyte count may be helpful because virtually all plague patients have an elevated blood count and percentage of PMNs plus PMN precursors. Antibiotic therapy may be warranted for patients with suggestive findings on physical or laboratory examination. The use of streptomycin, tetracycline and chloramphenicol is recognized to be effective against plague. Trimethoprim/sulfamethoxazole may also be used for the treatment of plague when all of the above drugs are contraindicated. The administration of gentamicin is probably effective treatment for plague although controlled trials have not been conducted.[13] In patients who are treated empirically with antibiotics a blood culture or acute and convalescent titers, or both, should be done to provide laboratory confirmation of the cause of the illness.

In summary, physicians practicing in the American West and physicians elsewhere treating patients who have been in the West within the past week should consider plague in the differential diagnosis of patients presenting with fever and gastrointestinal symptoms. These patients should be queried about residence in rural areas, outdoor activities and possible exposure to plague vectors, including wild rodents and free-roaming domestic dogs and cats. A differential leukocyte count may be helpful in raising the possibility of plague. Because of the high fatality rate of untreated plague and public health concerns related to secondary spread of the infection, prompt antibiotic therapy and appropriate isolation are warranted for patients who may have plague.

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Features of Potentially Reversibile Dementia in Elderly Outpatients

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A standardized evaluation was carried out in two separate groups of patients with dementia to determine the features that characterize those with potentially reversible or treatable dementia. In both groups, Alzheimer's-type dementia was the most common diagnosis (65% and 70%); the most common cause of potentially reversible cognitive impairment was medication toxicity. In both groups, patients with potentially reversible dementia had a shorter duration of symptoms, less severe dementia and used more prescription drugs. Because of this association, these features may be considered risk factors but are not distinguishing or diagnostic features of patients with potentially reversible dementia. Other, previously undetected, treatable illnesses not often considered in the differential diagnosis of potentially reversible or treatable dementia were also prevalent in these patients.

(Larson EB, Reifler BV, Sumi SM, et al: Features of potentially reversible dementia in elderly outpatients. West J Med 1986 Oct; 145:488-492)

A careful, systematic evaluation has been recommended for all patients with possible dementia[1-8] because some of these patients do not have dementia but another illness mimicking dementia[5] and because treatable diseases may cause potentially reversible dementia.[6,9] Therefore, a precise diagnosis of the type of dementia and its causes is of critical importance for effective patient care.

We recently found[10] that diagnostic outcomes of evaluating elderly outpatients with possible dementia differ somewhat from those reported in series containing primarily younger patients.[1,2,5,9,11-15] We also observed that patients with potentially reversible dementia showed improvement; many patients, however, did not revert completely to normal as they frequently had coexistent irreversible dementia. Nonetheless, the reversible condition had clearly caused excess disability. Comparison of clinical features of patients with potentially reversible and irreversible dementia showed group differences that could alert physicians to patients with unnecessary disability[10] if these differences were found in other groups of patients. In this paper we report the results of studies in another 200 patients to further define differences between patients with potentially reversible and those with irreversible dementia and, in particular, to determine if these differences are common to two groups of patients.

Patients and Methods

Case-selection criteria, the diagnostic evaluation and diagnostic criteria have been described previously.[10] In the first study, 107 patients were enrolled prospectively from 1978 to 1980[10] and in the second 200 from 1980 to 1982.[16]

All patients in the 1980-1982 sample met the following four entry criteria: (1) older than 60 years; (2) having possible global cognitive impairment on the basis of the patient or family complaining of symptoms such as forgetfulness, confusion, inability to care for self and slow thinking; (3) having symptoms for at least three months' duration, and (4) willing to undergo diagnostic evaluation and to participate in follow-up for at least one year after evaluation. Informed consent was obtained from patients, family members or guardians. Of 209 consecutive patients referred for evaluation between 1980 and 1982, 200 satisfied the enrollment criteria. Of the nine exclusions, five were too young and four did not agree to a follow-up.

Patients in the 1978-1980 sample met the first three entry

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ABBREVIATIONS USED IN TEXT

ATD = Alzheimer's-type dementia
DSM III = *Diagnostic and Statistical Manual of Mental Disorders*, third edition
SD = standard deviation
WAIS = Wechsler Adult Intelligence Scale

criteria. The diagnostic evaluation was done as part of their regular patient care. Consent to participate in follow-up was not obtained at the time of evaluation; follow-up information was sought for all patients one year after initial evaluation.

Evaluation

All patients were evaluated by an internist (E.B.L.) and a psychiatrist (B.V.R.). Internal medicine evaluations consisted of a complete history and a physical examination with formal neurologic examination including mental status testing. If possible, a family member or friend accompanied the patient to provide and verify details of the history. The Mini-mental State test[17] and the Dementia Rating Scale[18] were used for both groups. The psychiatric evaluation explored the problem areas as perceived by the patient and family and included detailed examination for dementia and depression using criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, third edition (DSM III).[19]

As part of the medical evaluation, all patients with possible dementia received a standard laboratory evaluation, including those tests recommended for evaluating dementia.[3,6] This evaluation has been described in detail elsewhere.[10,16]

Diagnosis

Diagnoses were based on the results of the original evaluation, diagnostic tests and a subsequent summary visit. In the 1980-1982 study group, diagnoses were reviewed and confirmed by a consensus group that reviewed the results of the history, physical and neurologic examinations; psychiatric evaluation; laboratory tests including computed tomographic scans; neuropsychologic tests—including the Wechsler Adult Intelligence Scale (WAIS), the Wechsler Memory Scale and Fuld Object-Recall tests—and a summary visit. The group included the internist who evaluated the patient, a psychiatrist, a psychologist, a neuropathologist-neurologist (S.M.S.) and the public health nurses (C.G.C., N.M.C.) who coordinated the evaluation and followed the patients.

Diagnostic criteria have been described in detail[10,16] and included the research diagnostic criteria[20] for organic brain syndrome (impaired orientation and memory plus one of the following: impaired calculation, attention, abstraction or comprehension and no evidence of delirium or impairment of consciousness). In general, the consensus group based the diagnosis of Alzheimer's-type dementia (ATD) on the criteria proposed by Eisdorfer and Cohen.[21] The guidelines were as follows:

- Loss of global cognitive function to a level that compromised a patient's ability to adapt to the environment;
- Progressive deterioration;
- Duration of at least six months;
- Absence of other illnesses causing dementia.

On mental status examination, the patient showed impairment in at least two of the following abilities: learning, attention, memory or orientation *plus* one of the following cognitive skills: calculation, abstraction and judgment and comprehension. All patients with a diagnosis of ATD had evidence of memory loss. Other causes of dementing illness were either excluded or listed as contributing causes of dementia if the patient was judged to otherwise have typical Alzheimer's-type dementia. Patients having ATD who also had signs of Parkinson's disease (rigidity, coarse tremor, bradykinesis, shuffling gait and the like) were diagnosed as having ATD with Parkinson's disease. If signs of Parkinson's disease preceded dementia or were predominant, patients were classified as having Parkinson's disease causing dementia. A diagnosis of multi-infarct dementia was based on a Hachinski ischemic score greater than 7 points[22] and excluded when the score was less than 4.[22] The diagnosis of a major affective disorder was based on DSM III criteria.[19]

Patients were classified as having potentially reversible dementia by the internist (E.B.L.) at the summary visit in the 1978-1980 group and by the internist with the consensus group confirmation in the 1980-1982 group. This classification was based on the investigator's assessment that the disease diagnosed caused cognitive impairment and that the cognitive impairment was likely to improve with appropriate treatment.

Follow-up

All patients in the 1980-1982 study group were followed for at least 12 months after evaluation. Outcomes were based on the overall clinical assessment and the results of neuropsychological testing including the Mini-mental State test, the Dementia Rating Scale, the WAIS, the Wechsler Memory Scale and the Fuld Object-Recall test. Follow-up information in the 1978-1980 study group was sought between 1980 and 1982 and was based on physician evaluations, an audit of medical records and interviews with family members or acquaintances of the patients. Improvement or "reversibility" in cognitive function was based on the findings of neuropsychological tests and reports from family members and caregivers. Objective improvement was defined as at least a 2-point change in the Mini-mental State score, at least 1.5 points on the Dementia Rating Scale or at least 10 points on the WAIS or Wechsler Memory Scale. The duration of improvement had to be at least one month to be considered more than just a change due to normal variation unrelated to treatment.

Data Analysis

Data were analyzed using Student's *t* test, analysis of variance and the χ^2 test for statistical significance.[23]

Results

Mean age ($\pm$ standard deviation [SD]) in the 1978-1980 group was 75.8 ± 8.1 years and 75.7 ± 7.5 years in the 1980-1982 group. The demographic features have been reported in more detail elsewhere[10,16] and were comparable in both groups. In the second group, 31% of patients were living alone at the time of evaluation, 44% were living with a spouse and 14% were living with another relative. Most patients (72%) lived in their own homes or apartments; 10% lived in unsupervised housing for the elderly, and only 8% were in nursing or convalescent homes at the time of evaluation. The mean duration of memory loss (as determined by asking a

family member or close acquaintance) was 42.0 months (SD =31.1). The mean Mini-mental State score was 19.1 (SD = 7.9, range 0 to 30, with the higher score reflecting less impairment), indicating that the severity of dementia varied, with the average patient being moderately demented.

The distribution of dementia diagnoses is shown in Table 1. Alzheimer's-type dementia was the predominant diagnosis and was associated with Parkinson's disease in 7 patients (7%) in 1978-1980 and 12 patients (6%) in 1980-1982. Other "irreversible" dementias included progressive supranuclear palsy, posthypoxic encephalopathy, Parkinson's disease associated with dementia and posttraumatic encephalopathy, among others. It was not uncommon for patients to have more than one condition that was judged to contribute to dementia; thus, there are more diagnoses than patients in both groups. Furthermore, a mutually exclusive classification was often difficult. For example, one patient with confusion due to chronic alcohol intoxication could also have been classified as potentially "reversible" for Table 1, especially because the confusion cleared with total abstinence. In addition, 29 patients (27%) in the 1978-1980 group and 48 (24%) in the 1980-1982 group were diagnosed as having coexistent depression and dementia.

The causes of potentially reversible or treatable dementia are shown in Table 2. In both groups, the most common causes were medication side effects followed by hypothyroidism. An overlap between the causes listed in Table 2 also presents a problem of classification because some metabolic abnormalities were medication side effects, such as insulin-induced hypoglycemia.

Patients classified as having potentially reversible dementia were compared with patients with so-called irreversible dementia. Features that were significantly different in patients with potentially reversible dementia in the 1978-1980 study group (shorter duration, less severe dementia and the use of more prescription drugs) were also significantly different in the larger 1980-1982 study group (Table 3). Drugs used significantly more frequently in the reversible subgroup were sedative-hypnotics ($P<.01$) and antihypertensives. Two differences appeared in the 1980-1982 group comparisons between potentially reversible and irreversible subgroups that were not present in the 1978-1980 comparison; patients with potentially reversible dementia were more likely to have a history of falling (50% versus 25%, $P = .008$) and were more likely to show previously undetected abnormalities of the feet on physical examination, such as debilitating ingrown toenails (40% versus 14%, $P<.001$).

The investigation of patients in both groups resulted in the diagnosis of a surprisingly large number of other medical diseases. The 1978-1980 group had 48 patients who had 88 other previously unrecognized but treatable diseases diagnosed, all of which were judged to be important clinically because they contributed to dysfunction or caused symptoms.[10] A total of 248 other medical diagnoses were made in the 124 patients in the second group.[16] Table 4 shows some of the more common, previously unrecognized but treatable illnesses diagnosed in both groups of patients. The miscellaneous category includes illnesses like metastatic breast cancer, seborrheic dermatitis, acne rosacea, decubitus ulcers, other forms of medication toxicity, hypertension and transient ischemic attacks, among others.

In the 1978-1980 group, 13 patients with potentially reversible dementia were evaluated at least six months after the initial evaluation, and 11 had improvement in cognitive function. In eight of these patients, however, persistent worsening consistent with an Alzheimer's-type dementia eventually developed. In the 1980-1982 group, 18 of 30 patients with potentially reversible dementia showed persistent improvement at one-year follow-up. Of these 18 with persistent improvement, 7 did not meet the criteria for objective improvement documented on psychometric tests but were judged

TABLE 1.—*Distribution of Dementia Diagnoses in 2 Study Groups*

Diagnosis of Dementia	1978-1980 (N=107) Number Diagnoses	1978-1980 (N=107) Patients, Percent	1980-1982 (N=200) Number Diagnoses	1980-1982 (N=200) Patients, Percent
Alzheimer's-type dementia	74	69	149	75
Multi-infarct dementia	4	4	3	2
Alcohol-related dementia	4	4	8	4
Other "irreversible" dementia	3	3	18	9
Potentially "reversible" dementia	15	14	30	15
Not demented	15	14	15	8
Totals	115		223	

TABLE 2.—*Causes of Potentially Reversible Dementia in 2 Study Groups*

Cause of Dementia	1978-1980 (N=107) Patients, Number	1980-1982 (N=200) Patients, Number
Medication side effect	5	19
Hypothyroidism or myxedema	4	6
Subdural hematoma	2	0
Other metabolic causes*	1	5
Other†	3	0
	15	30

*Causes included hyperparathyroidism (2), hypoglycemia (2) and hyponatremia (2). In both patients with hypoglycemia, this developed as a drug (insulin) side effect, and the use of diuretics undoubtedly contributed to hyponatremia in both patients with this metabolic cause.

†Transient ischemic attacks, rheumatoid vasculitis and manic-depressive illness associated with dementia syndromes.

TABLE 3.—*Features of Reversible Dementia in 2 Groups of Patients*

Features of Dementia	1978-1980 Reversible (N=15)	1978-1980 Irreversible (N=77)	1978-1980 P Value	1980-1982 Reversible (N=30)	1980-1982 Irreversible (N=155)	1980-1982 P Value
Duration, mo	28.5±15.7*	51.7±55.7	.01	33.7±24.0	44.1±32.4	.027
Severity of dementia†	20.0± 4.8	14.5± 7.8	.04	21.3± 8.0	16.3± 9.3	.001
Prescription drugs, number	2.5± 2.1	1.4± 1.4	.02	3.4± 2.1	1.7± 1.9	<.001

*Values expressed as mean ± standard deviation.
†Mini-mental State score.

"clinically" improved by family members and research nurses. Likewise, 7 of the 30 patients with potentially reversible dementia in the 1980-1982 group experienced transient reversal of cognitive dysfunction that did not persist at the time of one-year follow-up.

Discussion

Dementia is an extremely common disorder in the elderly.[24] Until recently, most series of demented patients have focused on younger patients.[1,2,5,9,11-15] This series confirms our original research[10] and the finding of Fox and co-workers,[25] among others, that ATD is the most common cause of dementia in this population. A more surprising finding is the paucity of mass or destructive central nervous system disease causing dementia in elderly patients. This difference may be related to the long duration of dementia in outpatients and to the relative infrequency of such illnesses as normal-pressure hydrocephalus, brain tumor and subdural hematoma; these are all rare diseases, especially in ambulatory patients, and have probably been overrepresented in hospital-based series of patients with dementia.[1,2,5,9,11-15,25] By contrast, conditions like Alzheimer's disease, hypothyroidism and medication toxicity are more common, do not necessarily result in hospital admission and, thus, predominate in our series of patients. Because dementia is more prevalent in elderly outpatients, studies of this group of patients should be of particular value to clinicians. These epidemiologic factors need to be considered in evaluating patients and in formulating diagnostic strategies.

The validity of dementia diagnoses is important in a study focusing on diagnostic evaluation. We prospectively established diagnostic criteria using the available literature. In addition, review of each case by a multidisciplinary consensus group provided another important validation step, given the clinical nature of most diagnoses. Finally, each patient in the 1980-1982 group was followed systematically to ascertain if the clinical course validated our initial diagnosis. We are not aware of other studies of the diagnostic evaluation of dementia that have taken such a systematic and arduous approach to validate diagnostic results. Even though newer criteria for ATD have been published[26] and Hachinski's criteria for multi-infarct dementia have been questioned,[27] our follow-up experience, including autopsy in more than 40 patients, has largely confirmed our clinical and consensus diagnoses[16] and has not produced any diagnostic surprises.

TABLE 4.—*Some Previously Unrecognized But Treatable Illnesses Diagnosed in 307 Patients Evaluated for Dementia, 1978-1982*

Treatable Illness	*Patients, Number*
Depression	87
Parkinson's disease	23
Low folate level	19
Osteoarthritis, rheumatoid arthritis, other arthritis	14
Urinary tract infection	12
Chronic obstructive pulmonary disease	9
Congestive heart failure	7
Iron deficiency anemia	5
Peptic ulcer disease	4
Other miscellaneous diagnoses	44

That is, all patients classified as having Alzheimer's-type dementia, multi-infarct dementia or another so-called organic dementia had a clinical course consistent with the original diagnosis. Autopsy findings invariably showed the presence of organic brain disease; preliminary analysis of autopsies done on patients with a clinical diagnosis of ATD indicates more than 90% autopsy confirmation of the diagnosis, although coexistent neuropathologic disease (Pick's disease, Parkinson's disease, multiple infarcts) was present in some cases (E. B. Larson, MD, unpublished observations, June 1986).

The consistency of features associated with potentially reversible dementia deserves comment. Freemon and Rudd also observed a shorter duration of symptoms in patients with reversible dementia.[28] Thus, all three studies that have systematically tried to determine features of so-called reversible dementia have reported this finding. Another consistent finding was that reversible dementia was characterized by less severe symptoms. Less severe dementia was also correlated with a short duration and these two features are, therefore, interrelated. The other feature of this group, that patients with reversible dementia used a greater number of medications, reflects the predominance of medication toxicity as a cause of potentially reversible dementia in this series. Future research to confirm this finding and to improve detection and prevention of drug toxicity in the elderly is important given the high frequency of medication use[29,30] and medication toxicity[31] in older patients. Falling was also correlated with medication toxicity and reversibility in this study; medications causing confusion, especially the common drugs responsible for medication toxicity in our series (antihypertensives and sedative-hypnotics) will also cause gait instability and postural hypotension. The curious finding that patients with reversible dementia had more abnormalities of their feet probably represents a marker of neglect and inability to care for self[32] because the abnormalities were typically ingrown or overgrown toenails.

These features of potentially "reversible" dementia obviously do not create non-overlapping subgroups nor do they "make" any unique diagnoses; rather, they are associations seen in a group of patients with diverse diagnoses. Furthermore, the potentially reversible causes of dementia are often found in patients with coexistent irreversible dementia, like ATD.[10] The diagnoses are usually suspected or made based on the recognition of clinical syndromes. If our findings are generalizable and confirmed by others, they may help clinicians detect these patients more effectively by heightening awareness and suspicion in patients with these features. The information could also be useful for persons working with confused geriatric patients if they wish to focus more diagnostic surveillance on high-risk subgroups of patients. We hope others will study these and related issues in different populations.

Finally, even though this article focuses on detecting potentially reversible or treatable dementia, we do not wish to imply that clinicians should direct their efforts only on detecting and treating these reversible illnesses. Most patients with reversible dementia do have improvement but only four patients from the two series returned to normal. Overall, 25% to 30% of patients in the two studies showed objective improvement in cognitive function during follow-up,[10,16] in-

cluding some patients with "irreversible dementia." Thus, improvement may occur in patients with irreversible dementia. The existence of a large burden of previously undetected other medical illnesses along with considerable social and psychological problems experienced by these patients indicates it is not wise to focus strictly on detecting potentially reversible dementia.[10] We believe that an attitude or statement implying that "there is nothing (more) we can do for you" after a dementia evaluation is perhaps the most discouraging and damaging message a patient and family can receive and usually is a barrier to effective patient care. Nonetheless, one goal of effective patient care should be to detect reversible conditions causing and exacerbating dementia, as these conditions are clearly part of the substantial burden of excess disability in elderly patients with dementia.

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Activated Charcoal—Past, Present and Future

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Poisoned patients were first treated with charcoal more than 150 years ago. Despite its almost universal acceptance today, activated charcoal's role has been overshadowed by the emphasis on treating poisoned patients first with gastric emptying. We review the current use of activated charcoal and recent studies that suggest that activated charcoal may be the single most effective treatment in many types of poisoning. New explanations for the mechanisms of action include "back diffusion" and disruption of enterohepatic loops. Clinical data endorse a new and aggressive role for activated charcoal in the management of poisoned and overdosed patients.

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Activated charcoal is widely used in the treatment of overdoses and poisonings in conjunction with gastric emptying. The use of charcoal in the treatment of poisoned patients had gained universal acceptance only during the past 20 years.[1] Its current usefulness has been limited primarily to a one-time dose usually administered in an emergency department setting. Recent evidence suggests that frequent and repeated doses of charcoal may be important for the victim of a serious toxic ingestion. Furthermore, oral charcoal administration only without prior gastric emptying may have a role in the management of some poisoned patients.

History

The adsorbent properties of charcoal were described in the 1700s, and the first clinical applications occurred in the early 1800s. Early investigators such as Bertrand, Tovery, Hort and Garrod showed the effectiveness of charcoal in preventing clinical effects of poisoning in animals and humans.[2,3] A classic and frequently cited early demonstration with charcoal was the ingestion of a lethal dose of strychnine mixed with charcoal by Tovery before the 1831 French Academy of Medicine. Tovery suffered no ill effects from the strychnine because of the simultaneous ingestion of charcoal.[3] Similarly, the American physician Hort, by administering oral charcoal, reportedly saved the life of a patient in 1834 who ingested mercury bichloride.[2]

Over the next 150 years, charcoal was further refined, purified and activated to improve its adsorptive powers. Numerous studies were published describing the adsorbing characteristics and potential clinical benefits of charcoal.[4,5] Despite this work, charcoal was not widely accepted as an essential tool in the management of poisoned patients until the past 20 years. A review article published in the *Journal of Pediatrics* in 1963 has been credited with stimulating the more universal use of charcoal in poisoned patients.[5] Despite the early recommendation that charcoal be given as a first-line antidote or mixed with lavage fluid, it is still frequently given only after gastric emptying has been completed by emesis or lavage.

Activated Charcoal

Activated charcoal can be prepared from one of a variety of carbon-containing materials.[6] Wood pulp with a low ash content, coal, lignite and rye starch are some examples of sources. Once the charcoal (nearly pure carbon) is obtained through chemical means, it is broken down into a fine granular form. To activate it, a further process of treating it with steam, oxygen, carbon dioxide, certain acids and other chemicals is undertaken. This activating process removes impurities and creates fine, small granules. As a result, currently used activated charcoal has a surface area of about 1,000 m^2 per gram, while experimental activated charcoal with surface areas of up to 3,500 m^2 per gram has been manufactured.[7] Activated charcoal will adsorb most drugs and toxins,[8,9] but not all compounds are well adsorbed (Table 1).[10]

Present Use

Activated charcoal is now widely used in the treatment of poisoning and overdoses but in conjunction with gastric emptying.[12] Gastric emptying is usually carried out by one of two means. In an alert and awake adult patient, syrup of ipecac is usually administered orally in a dose of 30 ml (smaller doses

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TABLE 1.—*Compounds Poorly Adsorbed or Not Adsorbed by Charcoal*

Alkali*	*N*-Methyl carbamate*
Boric acid*	Malathion*
Cyanide†	Electrolytes*
Dichlorodiphenyltrichloroethane (DDT)*	Water-insoluble compounds such as methanol‡
Ferrous sulfate*	Tolbutamide*
Mineral acids*	

*From Decker et al.[10]
†From Andersen.[2]
‡From Berlinger et al.[11]

in pediatric patients). This generally will induce emesis, but if it fails, the dose of ipecac may be repeated about 15 to 30 minutes after the initial dose. After the patient has finished vomiting, activated charcoal in a dose of about 1 gram per kg of body weight is administered orally to the patient.

Gastric lavage is carried out on patients who are not alert or who have a diminished gag reflex. Before the gastric tube is passed, the patient's airway must be protected, which requires positioning in the left lateral decubitus position and often requires endotracheal intubation. A total of 3 liters or more of fluid in small 200- to 300-ml aliquots is used until the return is clear (smaller amounts of normal saline solution can be used in pediatric patients to prevent hyponatremia).[13] Repeated lavage with warmed saline has recently been advocated.[13] After gastric lavage, activated charcoal can be placed directly through the lavage tube into the stomach. One should preferably attempt to achieve an activated charcoal-to-toxin or drug ratio of about 10:1.[14]

Following the administration of activated charcoal, cathartics are indicated to evacuate the charcoal-poison bonded complex from the gastrointestinal tract. The relative risks and benefits of cathartics have recently been reviewed.[15] Although the efficacy of cathartics in the treatment of poisoned patients has never been documented, they were recommended by most (20 out of 27) medical toxicologists surveyed.[15] With the use of repeated doses of activated charcoal in the treatment of a poisoned patient, cathartics have been used to reduce the charcoal-induced constipation that occurs in some patients.[16] The use of oil cathartics should be avoided.[15] Relative contraindications for saline cathartics (sodium, phosphate and magnesium salts) include renal disease, profound electrolyte imbalance, hypertension, bowel obstruction and congestive heart failure. Profound electrolyte and free water loss can occur with repeated or large doses of either saline or osmotic (sorbitol or lactulose) cathartics. Activated charcoal can now be purchased premixed in a sorbitol solution. This solution is particularly useful when a lavage tube is in place, saving mixing time and the potential mess of mixing.

Because activated charcoal administration follows gastric emptying, many people consider charcoal only a second-line agent in the treatment of overdoses and poisonings. This backseat role may be unjustified. First of all, ipecac-induced emesis results in a variable return of ingested poisons. One study found that less than 30% of the ingested substance was vomited even when ipecac was given immediately postingestion.[17] It has been shown that when delayed 30 minutes postingestion, ipecac-induced vomiting alone has only a limited effect on reducing the total absorption and peak concentrations of acetaminophen, aminophylline and tetracycline and is significantly less effective in reducing absorption compared with activated charcoal given alone at the same postingestion time.[18]

Additionally, giving ipecac may waste valuable time. It has been well established that activated charcoal is more effective the earlier it is administered to a poisoned patient.[1,18] The current emphasis on ipecac-induced vomiting may undermine this effectiveness. A delay of one to six hours[19] may ensue before charcoal can be administered because of the time required for ipecac to induce vomiting and the time of continued vomiting. Furthermore, if repeated doses of ipecac are necessary to induce vomiting, the administration of charcoal will be delayed further. Finally, it is not unusual for a patient to vomit the activated charcoal when given immediately after the cessation of ipecac-induced emesis. In a patient given gastric lavage, delays in administering activated charcoal are usually less and are more directly related to the actual time it takes to lavage the stomach and secure an airway.

New and Future Uses

Emesis and Charcoal

Recent studies have challenged the traditional approaches to a poisoned patient.[19–21] The use of only activated charcoal without prior emesis may be the most effective treatment modality for some types of poisonings. Activated charcoal has been shown to bind and prevent the absorption from the gastrointestinal tract of many ingested drugs and chemicals.

A recent study addresses the clinical usefulness of emesis in preventing aspirin absorption in adult volunteers. When ipecac was given alone and resulted in emesis, an approximate 30% reduction in salicylate absorption from control values was found compared with nearly a 50% reduction in absorption when activated charcoal alone was given. Subjects first given ipecac, then followed after cessation of emesis by activated charcoal also had only about a 30% reduction from control salicylate absorption. This was explained in part by the fact that eight of the ten subjects in this group immediately vomited the activated charcoal.[20] This experimental finding is consistent with clinical experience with combined emetic and activated charcoal therapy in overdosed patients.

In a recent study, more than 592 patients were randomly treated with either gastric emptying (emesis or gastric lavage, depending on clinical status) in conjunction with charcoal and cathartic, or with activated charcoal and cathartic alone.[19] No difference in mortality, morbidity or clinical outcome was found between the emesis and charcoal versus the charcoal-alone group. In obtunded patients, however, who presented within an hour after ingestion, those receiving lavage before charcoal had a better clinical course.[19] This must still be considered a preliminary study awaiting duplication in other centers with additional patients so that an analysis and comparison of the outcome of the two approaches with various toxic substances and categories of related drugs can be made.

In another study, dogs were used to further examine the relationship between gastric lavage and activated charcoal in the treatment of overdoses.[21] When dogs were administered 500 mg per kg of aspirin, followed 30 minutes later by activated charcoal, a significant reduction (17%) in peak salicylate levels compared with controls occurred.[21] Larger reductions (37%) occurred when gastric lavage preceded the

instillation of activated charcoal or when gastric lavage preceded and followed activated charcoal administration (48% reduction).[21]

Although the above studies tend to support the traditional concept of lavage before instillation of activated charcoal in obtunded patients, they suggest forgoing gastric emptying in an alert patient. Further studies in animal models with other compounds and further clinical trials with poisoned patients are needed to determine objectively whether gastric emptying followed by activated charcoal or activated charcoal alone is the best approach for various poisonings.

Effects of Gastrointestinal Charcoal on Systemic Drug Levels

A new and exciting role for the use of charcoal in poisoning has emerged. This is the concept of lowering serum concentrations of already systemically absorbed drugs or poisons. Two recent studies have shown the potential importance of activated charcoal in the gastrointestinal tract in reducing the serum half-life ($T_{½}$) of intravenously administered substances such as phenobarbital,[22] theophylline[11] and digoxin.[23] Although the exact mechanism of $T_{½}$ reduction is not known, nonrenal elimination was enhanced when activated charcoal was given orally after intravenous administration of either phenobarbital or theophylline to normal volunteers. The reduction in $T_{½}$ when activated charcoal was given orally approached 50% for both drugs compared with control values.

There are at least two possible explanations for this finding. Many drugs and toxins that undergo significant hepatic metabolism are conjugated with glucuronides or other substances—for instance, bilirubin, morphine, glutethimide and chloramphenicol—and then eliminated via the bile into the small intestines.[24] When these conjugates reach the gut, they can undergo hydrolysis by enzymes such as β-glucuronidase followed by reabsorption into the portal venous system (enterohepatic circulation) (Figure 1).[24] One explanation for the effects of charcoal would include the ability of activated charcoal to bind the conjugated drug before hydrolysis or the free deconjugated drug before reabsorption (Figure 2). Another explanation uses the concept of "back diffusion" of free drug from the systemic circulation across the gastrointestinal tract into the intestinal fluids and, finally, binding to the activated charcoal in the gut (Figures 2 and 3).[25] The equilibrium for "back diffusion" is strengthened by the characteristic of an "infinite sink" in the intestinal tract brought on by the large binding capacity of charcoal and by the use of repeated doses of charcoal, which replaces charcoal that has moved out of the gastrointestinal tract by intestinal motility (Figure 3).[25] Collectively, the use of repeated doses of activated charcoal to disrupt enterohepatic loops, strengthen back-diffusion of drugs into the gastrointestinal tract and hasten elimination has been termed "gastrointestinal dialysis" by some.[25] The use of this treatment for severe overdoses, including intravenously introduced drugs, is a major advancement in clinical toxicology.

Earlier data have shown that a single dose of activated charcoal given 30 minutes after an oral dose of the tricyclic antidepressant nortriptyline hydrochloride reduces blood concentrations.[26,27] Further reductions in peak concentrations and the amount of total drug absorbed (measured from calculations of the area under the time versus drug concentration curve) were noted when four repeated doses of activated charcoal were given 30 to 360 minutes after a single dose of nortriptyline in human subjects.[27] These limited data are the only experimental evidence regarding the potential efficacy of

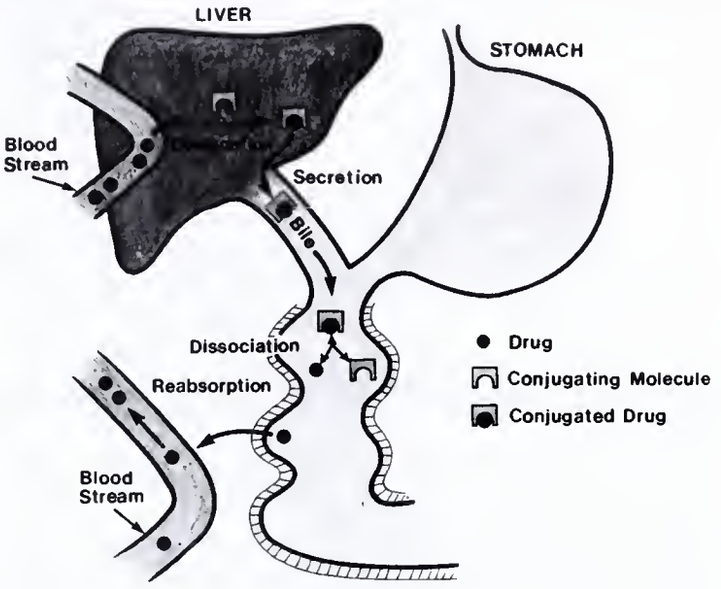

Figure 1.—Normal enterohepatic recirculation of drugs.

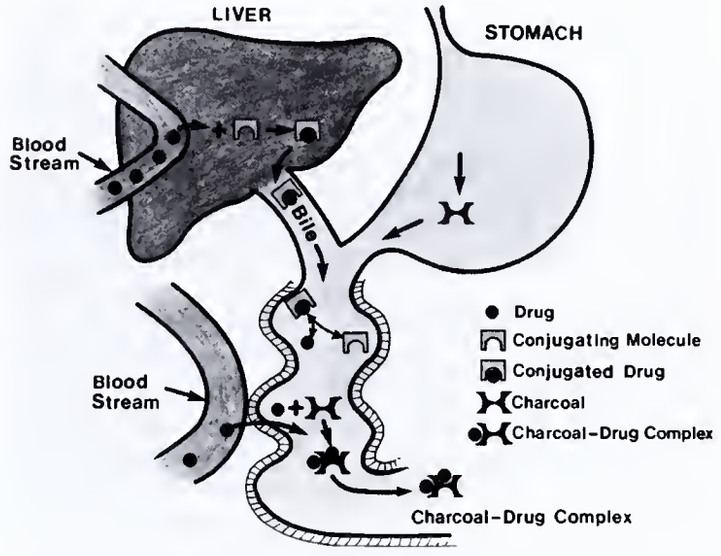

Figure 2.—Effect of charcoal on enterohepatic recirculation of drugs.

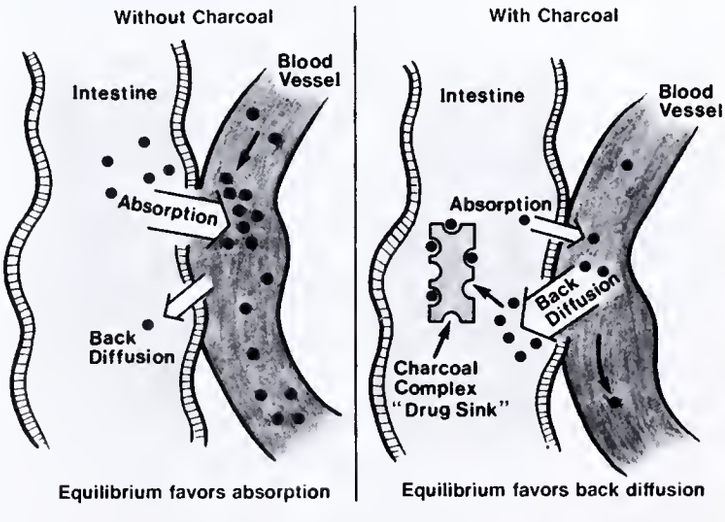

Figure 3.—Diffusion of drug with and without the use of charcoal.

repeated doses of activated charcoal in reducing the toxicity of troublesome overdoses of the tricyclic antidepressant.

A similar study has shown that the absorption of ingested carbamazepine (an anticonvulsant with a tricyclic structure), phenobarbital and phenylbutazone was almost completely prevented (>95%) when 50 grams of activated charcoal was taken within five minutes of the drugs.[15] Significant reductions in the total amount of drug absorbed were also noted when a single dose of activated charcoal was given one hour after drug ingestion.[15] When five doses of activated charcoal were given between 10 and 48 hours after ingestion of the drug, a 72%, 45% and 30% reduction (phenobarbital, carbamazepine and phenylbutazone, respectively) in $T_{½}$ was noted for the three drugs compared with the case with control ingestion.[15] Together, these experimental findings in humans would suggest that the oral administration of activated charcoal can reduce or prevent absorption of many ingested compounds when provided close to the time of drug ingestion. Further, repeated doses of activated charcoal can even, when started after several hours, reduce the $T_{½}$ of ingested or intravenously administered compounds.

A number of case reports have attested to the ability of repeated doses of activated charcoal to reduce the $T_{½}$ of digitoxin,[28] phenobarbital,[29] phenytoin,[30] dapsone[31] and theophylline.[32,33]

Recently, ten patients who were comatose after phenobarbital overdoses were randomly assigned to protocols that included a single dose of activated charcoal and sorbitol or repeated doses of activated charcoal and sorbitol.[34] All ten patients required intubation and mechanical ventilation. A greater than 50% reduction in phenobarbital $T_{½}$ was found in the group given multiple doses of charcoal compared with the single-dose group.[34] No significant reduction in the time on mechanical ventilator support or the total time of hospital stay was found, however, despite this dramatic reduction in phenobarbital $T_{½}$.[34] Thus, despite the small number of patients in this report, it points out the need for further critical examination in poisoned patients before the potential beneficial clinical effects of repeated doses of activated charcoal can be assumed.

Conclusion

Charcoal's effectiveness in treating poisoning occurs through its direct adsorption of the toxic substance in the gastrointestinal tract. In some instances, further benefit is gained through interference with enterohepatic or gastroenteral recirculation or back-diffusion (or both) of substance out of the systemic circulation across the gastrointestinal mucosa. Current evidence has drawn into question the routine use of emetics in the emergency treatment of mild overdoses in patients who are awake. Several lines of evidence reinforce the importance of the use of activated charcoal as the cornerstone of therapy for a poisoned patient. Current evidence suggests a continued role for lavage in more seriously overdosed comatose patients.

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Specialty Conference

Prevention of Renoprival Nephropathy

Discussant
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This discussion was selected from the weekly Grand Rounds in the Department of Medicine, the University of New Mexico School of Medicine, Albuquerque. Taken from a transcription, it has been edited by Ralph C. Williams, Jr, MD, Professor and Chair of the Department of Medicine.

PRATAP S. AVASTHI, MD:* In patients with chronic renal failure, finding a reversible disease or a reversible factor is crucial because correcting the reversible factor—such as obstruction, infection, hypertension—may allow recovery of some of the renal function. Regardless of the nature of the initiating disease, however, when renal function declines irreversibly to a certain level, the residual renal function tends to follow a progressive downhill course even if the original disease abates. If this additional progressive decline in renal function could be slowed and the need for eventual dialysis or transplant be postponed, clinically it would be an important step in the care of patients afflicted with an irreversible renal disease. The case reported here shows some of the approaches that are being used to reduce this kind of progressive loss of renal function. In this presentation, I will define the renoprival nephropathy, outline the body of evidence indicating that renoprival nephropathy exists and how it occurs and summarize the current recommendations to prevent renoprival nephropathy.

Report of a Case

The patient presented herein has been followed by the renal service at the Albuquerque Veterans Administration Medical Center for approximately ten years. This 65-year-old Spanish-American male restaurateur was first admitted to the University of New Mexico Hospital on December 6, 1975, for an acute episode of epistaxis associated with hypertension. He had been aware that he had high blood pressure for the previous nine years, but the degree of compliance with medication, adequacy of control and follow-up were not established. According to the patient, an intravenous pyelogram (IVP) done nine years earlier at another hospital had shown kidney disease. His family history revealed three siblings with hypertension

The patient said he had had no symptoms referable to the urinary tract. His medical history, however, showed several months of dysuria as a child. No medical evaluation or care was done for these symptoms. On physical examination his blood pressure was 230/160 mm of mercury and his pulse 75 per minute and regular. There were no signs of encephalopathy, the fundi showed grade 1 hypertensive change, peripheral pulses were normal, no abdominal or flank bruits were present and the cardiac examination showed a fourth heart sound but no evidence of congestive heart failure. No other abnormalities were found. Relevant laboratory values included normal findings on urine analysis, a chest x-ray film that showed left ventricular prominence and an electrocardiogram showing left ventricular hypertrophy with strain. A serum creatinine level was 2.4 mg per dl and creatinine clearance was 27 ml per minute; an IVP showed both kidneys to be small.

Hospital course: His blood pressure elevation was controlled with parenteral and later oral administration of antihypertensive medications. The hospital course was complicated by a subendocardial myocardial infarction and one episode of atrial fibrillation that converted to normal sinus rhythm with digitalization. Subsequently, he suffered no chest pain, congestive heart failure or cardiac dysrhythmias. The discharge diagnoses were renal insufficiency, cause unclear; hypertension, possibly due to renal disease, and subendocardial myocardial infarction.

In the intervening ten years, the patient has been followed in renal clinic with fair control of the hypertension. In the interim he had been admitted to hospital for many unrelated medical problems, given in Table 1.

The reciprocal of his serum creatinine for the duration is shown in Figure 1. During 1981 and 1982 when his blood pressure was high, the rate of decline in 1/serum creatinine accelerated. In May 1982, he was admitted to hospital and better control of his blood pressure was achieved. In anticipation of the need for dialysis, an arteriovenous fistula was constructed in his left forearm. He was started on a diet of 0.6 grams per kg protein, 2 grams sodium and 700 mg phosphorus daily and was followed in clinic. His subsequent renal

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ABBREVIATIONS USED IN TEXT

ACE = angiotensin-converting enzyme
IVP = intravenous pyelogram

functional state is shown in Figure 1. The most striking feature is the unchanged serum creatinine levels from 1983 to 1986 and the slope of the curve from 1978 to 1981 is very different from the slope of the 1/serum creatinine from 1983 to 1986. It should be added that the patient was a cook and showed remarkable compliance to the modified diet and to his prescribed medications.

Definition of Renoprival Nephropathy

A normal kidney has about 1 million nephrons. A variable percent of glomeruli and interstitial areas show scarring in older persons who have no history of having had any renal disease at any time.[1] One interpretation of this observation could be that in the absence of any detectable disease, although some of the normal nephrons die during the usual life span of a human being, the life span of most of the nephrons exceeds the average human life span. In contrast, when the total number of nephronal units is greatly reduced, the life span of the remaining normal nephrons declines and the nephronal attrition rate is increased. The nephropathy (resulting from a shorter life span of remnant nephrons) that occurs following a reduction in the number of nephrons (renoprival state) can be termed renoprival nephropathy.

Evidence of Renoprival Nephropathy

There are several lines of evidence to support the idea that following a large reduction in the number of nephrons, the remaining nephrons have a shortened life span. As is often true, the experimental evidence for the phenomenon is much more compelling than the clinical evidence.

Experimental Evidence

The clearest model for studying the phenomenon of renoprival nephropathy has been created by the surgical ablation of normal renal tissue, which leaves the remnant nephrons relatively undisturbed.[2,3] In rats left with 10% to 15% of the usual number of nephrons, instead of maintaining a stable state of azotemia, proteinuria and progressive glomerular sclerosis develop and they die of uremia. Additional experimental evidence has been generated by comparing the rate of nephron loss in spontaneous renal disease in New Zealand black/New Zealand white mice in two-kidney versus one-kidney animals.[4] Mice with one kidney had a far greater nephron-attrition rate, suggesting an extra destructive component superimposed on the disease process. Similarly, nephrotoxic serum nephritis in one-kidney rabbits resulted in a much more rapid rate of nephron loss.[5] Taken together, these studies show that a reduction in the number of functioning nephrons to below a certain number is associated with a dramatic reduction in the life span of remaining nephrons. Although this phenomenon may be species-specific,[6] at least for rats, rabbits and mice this observation seems to have been well established.

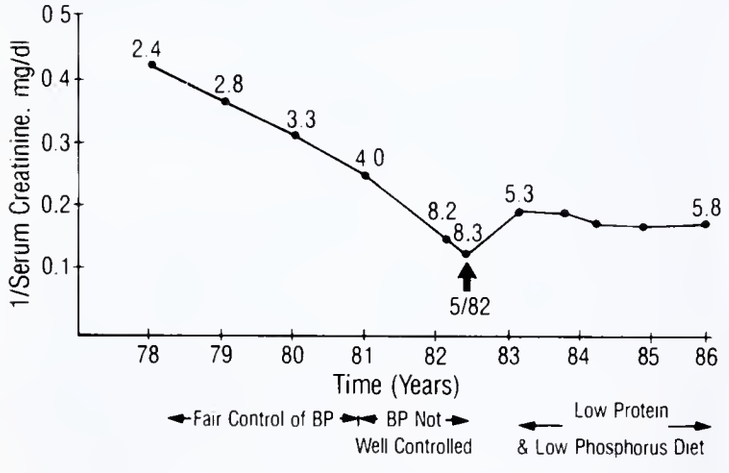

Figure 1.—The graph shows the plot of the reciprocal of serum creatinine (vertical axis) versus time (horizontal axis). Numbers indicate the serum creatinine values (mg per dl). The arrow indicates the time when arteriovenous fistula was constructed. Notice the difference between the slopes of renal function between the years 1979-1981 and 1983-1986. BP = blood pressure

Human Evidence

In humans, evidence for the hypothesis that the life span of nephrons is linked to their number is indirect. The observations listed below may support the hypothesis:

- Following a self-limited one-time injury, such as ischemic acute cortical necrosis, many patients will recover renal function only to have eventual slow progression to irreversible end-stage renal failure.[7]
- Some patients with analgesic nephropathy who have increased serum creatinine concentrations continue to show progressive renal damage despite discontinuing the analgesic intake.[8]
- Patients with high-pressure vesicoureteral reflux may continue to have deteriorating renal function despite a return to normal urodynamics following surgical correction.[9]

Although these observations are consistent with the hypothesis that a reduced number of nephrons shortens the life span of the normal nephrons left behind, they certainly do not conclusively prove it. If the hypothesis is correct, it may explain the progressive nature of renal failure regardless of the activity of the original disease process. The steady decline of renal function enables us to predict the relationship between 1/serum creatinine and time.

How Does Renoprival Nephropathy Occur?

The level of function of each nephron appears to be inversely proportional to the total number of nephronal units. For example, unilateral nephrectomy, which halves the number of nephrons, is followed by increased function of the

TABLE 1.—*Hospital Admissions From 1978 Through 1983*

Date	*Reason*
January 1978	Lower gastrointestinal bleeding
July 1980	Mucoepidermoid carcinoma of right superior alveolus
January 1981	Curettage of right maxillary sinus and control of blood pressure (BP)
January 1982	Control of BP (230/150 mm of mercury)
April 1982	Control of BP (220/110 mm of mercury) Placement of arteriovenous fistula
December 1982	Right maxillectomy
July 1983	Unstable angina
August 1983	New-onset atrial fibrillation

remaining nephrons.[10] Conversely, when the total number of nephrons is increased by transplantation of a third kidney in a normal animal, the functional level of all nephrons declines,[11] but this observation is controversial.[12] At least in adult animals, the compensatory increase in function following a reduction in nephronal number appears to be mostly from hypertrophy and not from hyperplasia.[13] Both glomerular (filtration) and tubular functions increase in parallel.[14] The compensatory hypertrophy appears to be roughly inversely proportional to the number of the residual functional nephron units. Evidence is accumulating to show that this short-term gain of compensatory hypertrophy is followed by a shortened life span of the remaining normal nephrons.

Components of Nephron Hypertrophy

In Experimental Animals

Experimentally induced hypertrophy of individual nephrons consists of an increase in both glomerular and tubular size and function. The increase in glomerular blood flow and pressure has been shown to occur in rats following nephrectomy.[10] Associated with the glomerular capillary hypertension, structural changes have been found in the glomeruli, and it has been postulated that the shortened life span of nephrons results from the local hypertension in the glomerular capillaries.[15] Evidence favoring such a mechanism has been put forth in experimental studies in which diabetic rats or rats with one sixth of their kidney mass are given angiotensin-converting enzyme (ACE) inhibitor to lower both systemic hypertension and glomerular capillary hypertension. They have less glomerular sclerosis and proteinuria compared with similar rats treated with conventional antihypertensive drugs, which lowered the systemic blood pressure to equal levels but failed to reduce glomerular capillary hypertension to the level of ACE inhibitor-treated rats.[16-17] These observations suggest that the glomerular hemodynamic adaptations arising from the renoprival state may contribute to premature demise of the remaining nephrons. It should be pointed out that although improved glomerular morphology and reduced proteinuria have been reported with ACE inhibitor, it has not been reported whether the renal function is also preserved. In another cell system (cardiac myocyte), the three phases of cell hypertrophy are followed by progressive cell damage.[18] A similar sequence of events may occur in the hypertrophied renal tubular epithelial cells, and the short-term gains of compensatory hypertrophy may lead to early demise of nephrons in the long run. While hemodynamically mediated damage has attracted a great deal of attention, it is possible that hypertrophy of tubular cells, per se, triggers the chain of events leading to the early death of nephrons. Our understanding of the mechanisms causing the compensatory tubular cell hypertrophy is limited,[13] but conditions in which tubular cell hypertrophy occurs are listed in Table 2.

In Humans

In humans, the loss of nephron mass (renoprival state) is followed by structural and functional hypertrophy of both glomeruli and tubules of the remaining nephrons.[19] It has been suggested that the increased hemodynamic stress mediates the renoprival nephropathy.[10] Once again, the evidence is indirect, and because increased glomerular pressure and tubular cell hypertrophy occur concomitantly and are not dissociable, it is not known which of these two events or whether both lead to a shorter life span of surviving nephrons. Because dietary intervention is used clinically to prevent progression of renal disease, I will examine the renal hemodynamic effects of dietary constituents in greater detail in humans.

For the past five years, we have been developing and testing a system for noninvasive direct measurement of renal blood flow. The method uses a combined two-dimensional echo real-time imaging system to locate the abdominal aorta and renal arteries and a range-gated pulsed Doppler flowmeter. After the walls of renal artery are defined along the longitudinal axis, Doppler signals from the entire lumen of the vessel are obtained by electronically varying the size of the sample volume and placing it in the arterial lumen (Figure 2). A schematic of the instrumentation set-up is shown in Figure 3. From the images and waveforms, vessel diameter, Doppler angle and Doppler frequency shifts are measured using fast Fourier transform. From these measured variables, the average velocity of flow can be calculated using the following Doppler equation:

$$\bar{V}\,(\text{cm per second}) = (\Delta f \cdot C)/(2 \cdot F \cdot \text{Cos}\,\theta)$$

where $\bar{V}$ is the spatially averaged velocity, Δf is the Doppler frequency shift, C is the velocity of sound in blood, F is the transmitted sound frequency and θ is the Doppler angle.

TABLE 2.—*Conditions and Hormones That Induce Renal Hypertrophy*

Nephron loss	Hypokalemia
High-protein diet	Metabolic acidosis
Diabetes mellitus	Testosterone
Pregnancy	Mineralocorticoids

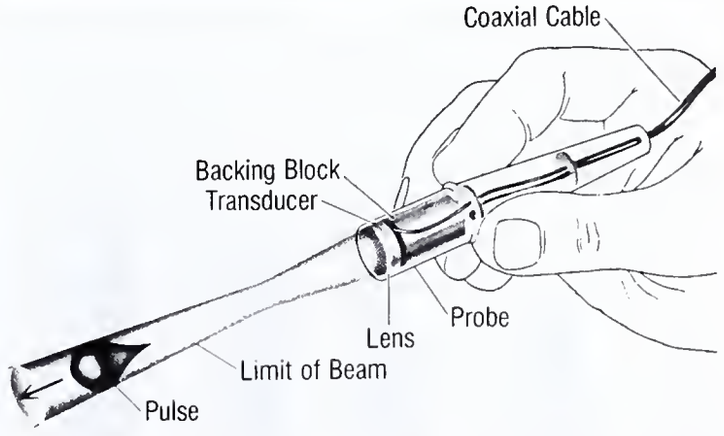

Figure 2.—The schematic shows a Doppler probe with a Doppler beam axis. A pulse of sound energy is transmitted along the axis into tissues and is received back. By varying the time interval between the transmission and reception, the depth of interrogation is varied.

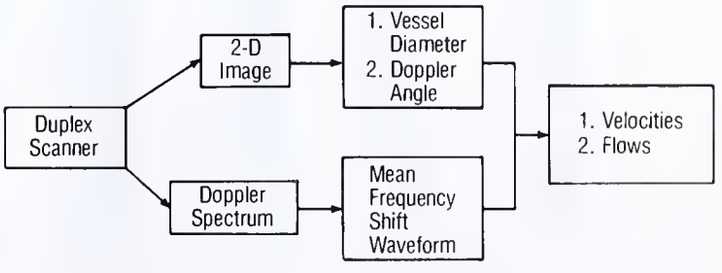

Figure 3.—The schematic shows the instrument set-up used in measuring the flow velocity from the vessels. 2-D = two-dimensional

From temporally averaged velocity (over a minimum of five cardiac cycles) and vessel diameter, a continuity equation allows the volumetric blood flow to be calculated as follows:

$$\dot{Q}\ (\text{ml per minute}) = [(\pi \cdot D^2 \cdot V)/4] \times 60$$

We have tested this method in vitro and in vivo for accuracy and linearity.[20,21] The possible clinical and research applications of this method in the renovascular system and references are given in Table 3.

Using this method, we have shown that in normal humans the acute postprandial increase in renal blood flow is sustained longer with the ingestion of protein (Figure 4).[25] Studies are planned to assess whether a low-protein diet can decrease renal blood flow in patients who have renal disease and who may already have a maximally dilated renovascular system as a part of compensatory hypertrophy. In such a state, a reduced protein intake may not be associated with a vasoconstrictive response by the renovascular system. Ingestion of a high-protein meal causes less increase in the glomerular filtration rate in diseased kidneys.[26,27] If renal blood flow in diseased kidneys similarly does not decline with the long-term reduced protein intake while the kidney function is preserved, the dissociation between the hemodynamics and progressive renal damage may indicate that factors other than increased hemodynamic stress are involved in renoprival nephropathy.

Whatever the mechanisms, restriction of dietary protein in patients with moderately increased serum creatinine levels appears to retard the progression of renal failure.[28,29] At present, it is uncertain whether this beneficial effect occurs via the reduced hemodynamic stress or whether protein restriction limits the compensatory tubular cell hypertrophy and thereby lengthens the life span of nephrons (Figure 5). Several studies have shown that dietary protein restriction to 0.6 grams per kg per day slows the progress of renoprival nephropathy.[28,29] Perhaps the case under discussion is an example of the same occurrence. Ketoanalogues of essential amino acids have been shown to similarly retard the relentless progression of renal failure,[30] but a comparative study of the efficacy of 0.6 mg per kg protein versus ketoanalogue substitution has not been done.

In addition to protein, severe limitation of dietary phosphate intake has been shown in animals to independently reduce the progression of renoprival nephropathy.[31] In studies in humans, a combined approach of protein and phosphate restriction has been used, and the results indicate that the renoprival nephropathy can be slowed.

TABLE 3.—*Ultrasonic Flowmetry of Renovascular System*

Clinical Applications
Diagnosis and follow-up of renal artery stenosis*
Diagnosis and follow-up of renal vein thrombosis†
Research Applications
Renal blood flow measurements†
Characterization of renovascular impedance and harmonic analysis

*From Avasthi et al.[22]
†From Avasthi et al.[23]
‡From Greene et al.[24]

Current Recommendations

Based on the foregoing considerations, the following dietary recommendations can be made for patients with chronic renal failure. These recommendations are in addition to the usual conservative management of chronic renal failure:

- In patients with continually above-normal serum creat-

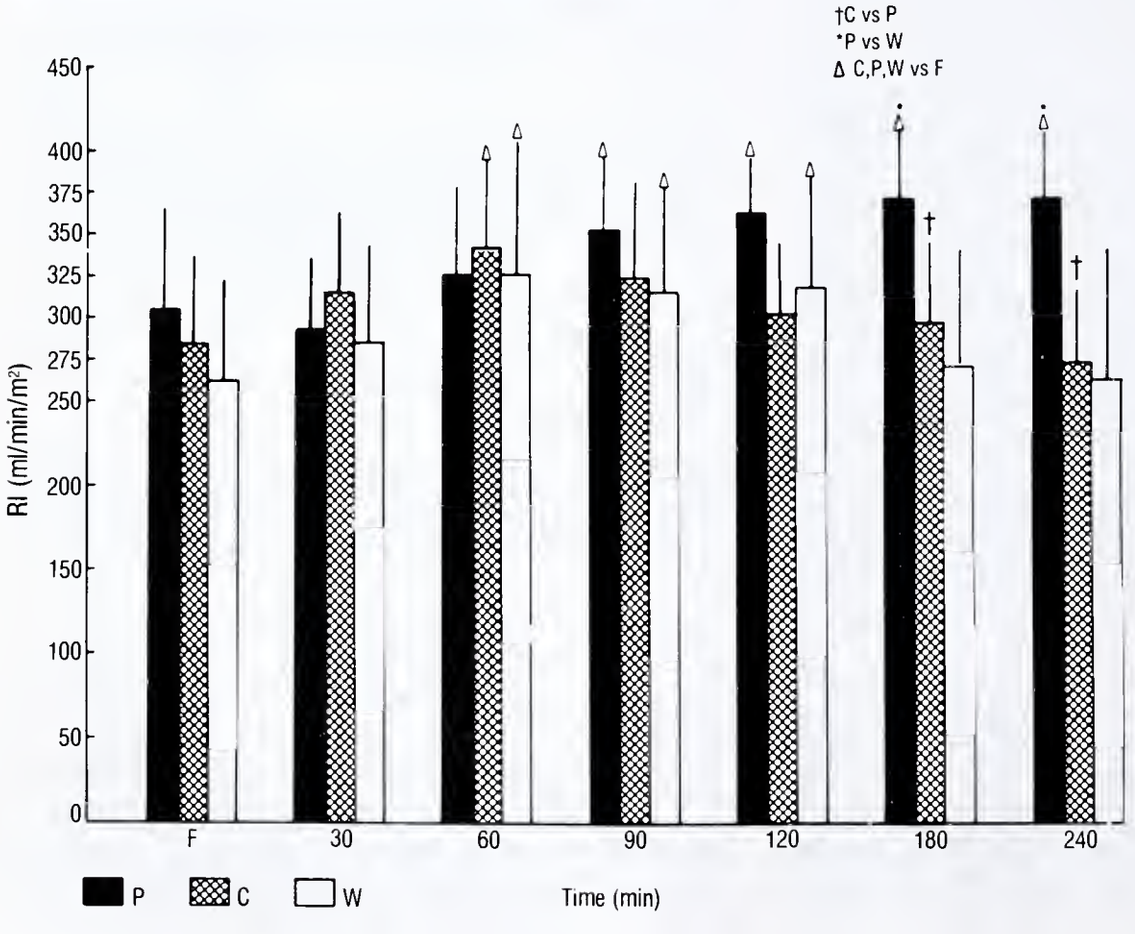

Figure 4.—The graph shows the renal blood flow (RBF) index (RI = RBF [ml per min] per m^2 body surface area) versus time at fasting **(F)** and at 30, 60, 90, 120, 180 and 240 minutes following a test meal containing 150 grams protein **(P)**, 150 grams carbohydrate **(C)** or an equal volume of water **(W)**. Statistically significant values (by analysis of variance) are denoted at the top of bars by the symbols (right upper corner). Note the longer duration of increased blood flow with protein.

inine levels, a daily diet with a protein content of 0.6 grams per kg and 700 mg phosphorus is advised to retard the rate of progressive renal failure.

• In patients with renal failure who have heavy proteinuria, it is unclear whether similar dietary recommendations should be made. Although one study has suggested that dietary protein restrictions do not reduce albumin pool size and therefore may not be detrimental to patients with nephrosis,[32] at present the issue has not been directly examined. Therefore, in such patients with high serum creatinine levels, adding protein to the above diet equal in amount to the daily urinary protein losses may be considered.

Although doubts have been raised about the efficacy of dietary intervention for conserving renal function, in our present state of knowledge, these recommendations seem justified till proved otherwise.[33]

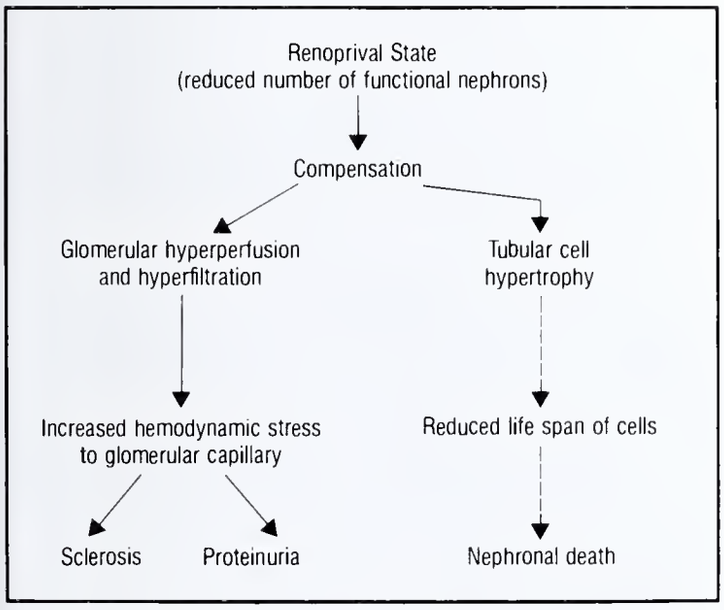

Figure 5.—A schematic representation of events in renoprival nephropathy. The arrows with broken lines indicate hypothetical mechanisms that have not been examined.

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Downwind Update—A Discourse on Matters Gaseous

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD:* *In opening this Medical Staff Conference, I do not know exactly how to announce the topic for discussion. It is "Downwind Update—A Discourse on Matters Gaseous." There is only one member of the faculty who would submit a title of that significance, and this is David F. Altman, Associate Clinical Professor of Medicine and Associate Dean, Director of the Gastrointestinal Clinic.*

DAVID F. ALTMAN, MD:† I would like to begin with an explanation of this conference's title. Many attempts have been made to find a suitable word for passage of flatus. I found the term "downwind" in a British medical publication, and I suggest it is both significantly genteel and evocative to pass muster, so to speak. My purpose is to bring you up to date on an area in which our understanding has literally exploded in the past several years.[1]

The normal gas content of the intestinal tract is about 200 ml, with more than 99% being one of five principal gases: nitrogen, oxygen, hydrogen, methane and carbon dioxide. The sources of this gas may be the swallowing of air, intraluminal production of gas and diffusion of gases from blood into the intestinal lumen. I would like to discuss briefly the genesis of each of these gases and their possible sources before considering the disorders of gas production.

Genesis of Intestinal Gases

The relative contribution of air swallowing to the genesis of intestinal gas is not clear. If one estimates that with each maneuver we swallow even as little as 2 to 3 ml of air, that alone would lead to the accumulation of many liters of nitrogen in the stomach over the course of a 24-hour period. Only about 400 ml of nitrogen is passed per rectum daily, however, and there is essentially no net absorption of nitrogen in the small bowel. So it is probable that air swallowing has very little to do with the amount of gas present in the gastrointestinal (GI) tract. In addition, as opposed to inspired air, of which nitrogen is approximately 80%, the range of nitrogen in intestinal gas is from as low as 10% to more than 90%, suggesting that diffusion of nitrogen from blood to the intestinal lumen may be more important than air swallowing in producing the gas that comes out of the lower end.

Finally, the anatomy of the stomach and the esophagus may play a role in influencing the amount of intestinal gas. The esophagus enters the stomach at its posterosuperior aspect. If a person is supine, swallowed gas, which of course tends to rise, cannot reflux up the esophagus. So a person who is supine cannot eructate any swallowed gas, and in this position air is more likely to pass into the duodenum. This position or posture may have an effect on how much swallowed air gets into the small bowel.

There are many sources of carbon dioxide in the gut. Carbon dioxide can be produced by the interaction of hydrogen and bicarbonate: 22.4 ml of carbon dioxide is produced per milliequivalent of bicarbonate. Given that hydrogen production after meals in a normal person can be about 30 mEq per hour, and that the digestion of triglycerides to fatty acids yields about 100 mEq of bicarbonate per 30 grams of fat, there is the potential for several liters of carbon dioxide to form in the duodenum after each meal. Thus, we are fortunate that carbon dioxide is readily absorbed from the upper intestine. Most of the carbon dioxide in flatus is derived from bacterial fermentation. Whether this is direct production of carbon dioxide by the bacteria or a by-product of their production of short-chain fatty acids that then can interact with bicarbonate is not clear.

With respect to hydrogen, bacterial metabolism appears to be the sole source of its presence in flatus. Most of the hydrogen is produced in the colon. Hydrogen excretion represents a balance of production and catabolism by bacteria for, in fact, colonic bacteria can consume hydrogen as well as produce it. This may be species specific, as administration of antibiotics has caused increased molecular hydrogen excretion, possibly because the antibiotics have inhibited specific hydrogen-catabolizing flora.

There is an excellent correlation between breath hydrogen

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ABBREVIATIONS USED IN TEXT

GI = gastrointestinal
P_{CO_2} = partial pressure of carbon dioxide
P_{N_2} = partial pressure of nitrogen

excretion and colonic hydrogen production, allowing very careful measurement of the effect of various conditions on hydrogen production in the gut. Breath hydrogen measurement is widely available now in clinical practice.[2]

Hydrogen production in the colon appears to be based on the incomplete absorption of carbohydrate and protein, with these then providing convenient substrates for bacteria in the colon. There are several mechanisms whereby carbohydrate and protein can arrive in the colon. The first is malabsorption. Most healthy adults do not absorb well simple carbohydrates such as lactose and the starches in wheat flour, oats and corn. In fact, only rice flour is completely digested in normal persons, as indicated by breath hydrogen excretion after ingestion of various flours.

Oligosaccharides and polysaccharides, which are not digested by small bowel enzymes, are then available to intestinal bacteria for the production of hydrogen as a by-product of fermentation. The clearest examples of this are the two oligosaccharides raffinose and stachyose. These are the carbohydrates that are present in beans and are the cause of the increased flatus that is the result of bean ingestion.[3]

In studies that have looked at the relative flatulence potential of several varieties of beans, soybeans—which are a prominent dietary constituent in many parts of the world—have led the list. There are ongoing attempts to develop a species of bean, particularly the California small white bean, that does not have stachyose and raffinose, but so far these efforts have not been successful.

There are a number of other poorly digested polysaccharides that can occur in our diets. Sorbitol has been widely used as a bulk sweetener in, for example, a number of sugarfree gums and mints. It is also found naturally in some fruits. In both normal and symptomatic persons—that is, those with complaints of gas and bloating—increasing oral doses of sorbitol caused increasing breath hydrogen production.[4] It is possible that some persons are particularly sensitive to sorbitol's effects.

Some gases in the intestinal tract are diffused out of blood. Diffusion of gas follows partial pressure gradients of gases between the gut lumen and blood. Gases generally are soluble in both lipid and water so that there is even diffusion across these partial pressure gradients. The partial pressure of hydrogen and methane is always greater in the lumen of the gut than in blood, so there will always be net diffusion of hydrogen and methane into blood. That is why pulmonary excretion of hydrogen and methane are good measurements of intestinal gas production. The partial pressure of carbon dioxide (P_{CO_2}) is generally higher in the blood than it is in the stomach, but as carbon dioxide is produced in the duodenum, the P_{CO_2} rises to a level greater than that in blood and a net diffusion of carbon dioxide occurs in that direction. The same occurs in the colon. Nitrogen has a slightly higher partial pressure (P_{N_2}) in the stomach than in the blood and tends to diffuse into blood there, but in the duodenum the nitrogen is diluted by carbon dioxide so that the P_{N_2} tends to fall and, therefore, in the duodenum nitrogen tends to diffuse back into the bloodstream. The same is true for the colon where carbon dioxide, hydrogen and methane tend to dilute out the nitrogen and, therefore, encourage diffusion of nitrogen from the colon into the bloodstream. The maximum gradient of partial pressure of nitrogen that has been measured is about 400 mm of mercury, which enables diffusion from the blood to the gut lumen of about 100 ml of nitrogen per hour. Only 16 ml per hour is necessary to account for the 400 ml of nitrogen that is passed per day; thus, it is impossible to determine how much flatus nitrogen is swallowed, how much is diffused and how much, if any, is produced in the gut. What we are left with is a relatively complicated picture of a balance between production and diffusion of gases in the gut, which is summarized in Figure 1.

There is a socially important aspect of intestinal gas production that I have not mentioned. The various gases I have discussed are all odorless and colorless. Less than 1% of all intestinal gas produced probably causes 99.9% of the trouble. These are the volatiles—a number of trace gases, most of which have not yet been fully characterized. These include ammonia, hydrogen sulfide and short-chain fatty acids. It is

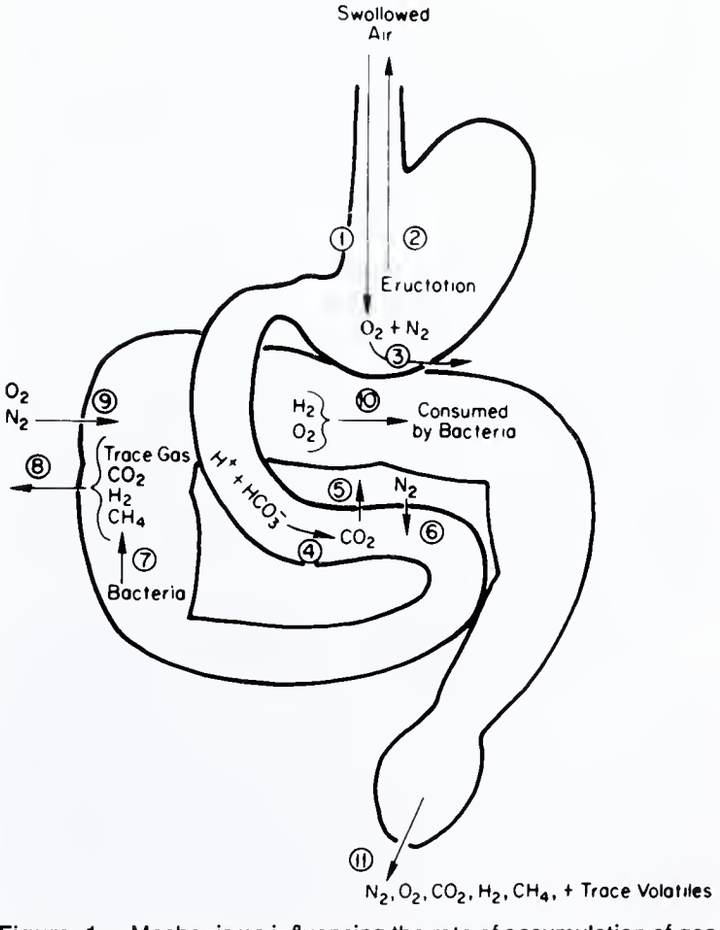

Figure 1.—Mechanisms influencing the rate of accumulation of gas in the gastrointestinal tract. Air is swallowed **(1)** and a sizable fraction is then eructated **(2)**. The oxygen (O_2) of gastric air diffuses into the blood draining the stomach **(3)**. The reaction of hydrogen ion (H^+) and bicarbonate anion (HCO_3^-) yields carbon dioxide (CO_2) **(4)**, which rapidly diffuses into the blood **(5)**, while molecular nitrogen (N_2) **(6)** diffuses into the lumen down a gradient established by the CO_2 production. In the colon, bacteria produce CO_2, molecular hydrogen (H_2) and methane (CH_4) **(7)**, which diffuse into the blood perfusing the colon **(8)**. Bacteria also consume O_2 and H_2 **(9)**. N_2 diffuses into the colon **(10)** down a gradient established by bacterial production of CO_2, H_2 and CH_4. The net result of all these processes determines the composition and rate of passage of gas per rectum **(11)** (from Johnson[5]).

likely that colonic anaerobic bacteria are responsible for the production of much of the volatile gases, but it has also been suggested that some of the odor is related to dietary constituents. In a recent study the gases produced when coprolites are rehydrated were examined with gas chromatography.[6] Coprolites are stone-age fecal material found in caves in many parts of Africa and the Middle East. These coprolites can be used to study what ancient humans ingested in their daily lives. By rehydrating them, one is able to determine what volatiles are present. Studies comparing modern-day feces with these coprolites and with animal feces have led to the recognition that much of this volatile material is directly related to components of the diet. For example, licorice has been found to be a major dietary constituent of the ancient Indians of the Southwest United States. There is still much to be learned about these components of intestinal gas, however.

Clinical Effects

First, where do bowel sounds come from? Most of the bowel sounds in normal persons are generated in the stomach and in the colon. When fluids are infused into the intestine via a tube, there is some generation of bowel sounds, but when an air-liquid mixture is introduced, the bowel sounds are much louder and much more active.[7] I have called this the waterbed phenomenon: If you have bubbles in a waterbed, it is going to be quite noisy, but if you get all the air out of the waterbed, it is relatively silent. It is the same for the GI tract. If there is more gas in the GI tract, the bowel sounds will be more prominent.

Gas has had its entertainment value, as well. For history buffs, there is an interesting story of one Joseph Pujol who was an entertainer in the Moulin Rouge in Paris in the late part of the 19th century.[8] It has been said that Pujol earned more per week than his contemporary Sarah Bernhardt, one of the great ladies of the stage. Pujol went by the stage name of Le Petomane. Apparently he entertained at the Moulin Rouge for a number of years by actually being able to play tunes using flatus. He was famous for a 15-second "aria" that imitated the tearing of calico. He also could extinguish a flame a foot away. I imagine that Pujol will go down in history as one of the great entertainers of all time.

Functional abdominal pain is clearly a problem for many patients and a major headache for gastroenterologists and internists. Patients often come to us with complaints of bloating and excessive gas. Walter Alvarez, one of the great physiologists of the early part of this century, subjected himself to serial abdominal x-ray studies and wrote, "When I thought I was full of gas there was no sign of it in the bowel, and when I was comfortable the roentgenogram sometimes showed the splenic flexure to be greatly distended." Levitt and colleagues looked at the amount of gas and its distribution in both normal persons and those complaining of excessive gas.[9] Using an argon washout technique, they found that in the controls the total volume of gas averaged 199 ml and in patients with excessive gas the average was 176 ml. The accumulation rates and composition were the same in the two groups. When the patients with intestinal gas complaints had the inert argon infused into the gut to wash out the active gases, they tended to have more of that inert gas reflux back into the stomach from the area of the ligament of Treitz where the gas was being infused. In addition, these persons commonly complained of severe pain during the gas infusion. Levitt and associates suggested that patients with problems of bloating and excessive gasiness may actually have abnormal small bowel motility and that the motility disorder might interfere with what would be the orderly passage of gas through the small bowel.

Another major complaint in these patients is the passage of excessive flatus. However, when Levitt and co-workers asked seven normal persons to chart over a period of a week how many times they passed flatus per day, they arrived at the number 13.6 ± 5.6. This is the closest number we have to what may be the normal number of passages of flatus per day.[10] I cannot tell you how important this number may be in clinical practice. When a person sees a physician complaining of excess flatus passage and is asked, "How many times a day do you pass flatus?," if the answer is eight or ten, the physician can say, "Do you know what normal is?" and quote this number. Levitt and associates also studied a 28-year-old man who was documented to average 34 passages of flatus per day, and he was measured as passing more than 1,300 ml of gas in a four-hour period, of which 82% was hydrogen and carbon dioxide.[10] When the patient followed an elimination diet, he kept a diary of both the number of passages of flatus per day and what he was eating, and he was able to identify particular foods that were the source of particular problems for him. Eliminating lactose from his diet decreased his flatus passage by about half. He found that a number of other foods were what he called extremely "flatogenic." These included the obvious—onions, beans and so forth—but also included celery, carrots, raisins, brussel sprouts, bananas, apricots, prune juice, pretzels, bagels (!) and wheat germ. With the elimination of these various foods, the patient's condition was much improved. The safest "food" that this man came across was water.

There are some therapies that we can offer our patients who have excessive problems with gas. The first is the elimination of lactose. Lactose intolerance and lactose deficiency are probably the most important causes of functional GI complaints. For those persons who are wedded to milk, a number of preparations are now available "over the counter" that can be added to milk and that break down the lactose to its monosaccharides glucose and galactose. Legumes may next be excluded. Then the elimination of wheat flour or oat flour with the substitution of rice or other glutenfree flours may also be useful for persons with intestinal gas that is refractory to these other measures.

Despite the suggestion that motility disorders may be important in the genesis of symptoms of excess intestinal gas, anticholinergics have not been effective in patients with these complaints. Metoclopramide may be helpful in some patients, but the number of patients studied has been small. Another possible help in patients with excess gas is activated charcoal, which can absorb gases. This may be useful when the charcoal is taken with meals.

Levitt and Duane reported in 1972 that 10% to 15% of healthy adults consistently passed stools that float.[11] We have been taught in medical school that floating stools is one of the cardinal signs of fat malabsorption. Yet, in the studies of Levitt and Duane, stools that floated were not different in fat content from those that did not. In fact, stools that float sink when the gas volume in the stool is compressed in vitro,

suggesting that it is the gas in the stool rather than the fat that may be most important. This might be called the Ivory soap phenomenon. Levitt and Duane also noted that persons who were most likely to have floating stools were those who are likely to be methane producers. Only about 33% of North American and European adults actually produce methane in their intestinal tract. It appears that the most responsible bacteria are highly anaerobic bacteria, principally *Methanobrevibacter smithii*. Bond and Levitt reported that methane production in the gut is a familial trait.[12] When both parents are methane producers, 92% of the children are methane producers, and 84% of the siblings of a methane producer will be methane producers as well. Methane production interestingly can occur in the fasted state and may be the result of catabolism of endogenous glycoproteins.[13]

Carbohydrate-poor glycoproteins are preferential substrates for methane production, whereas carbohydrate-rich glycoproteins tend to lead to hydrogen production. Methane production also tends to be highly pH sensitive so that when the pH is less than 7, methane production tends to fall. Thus, if increased hydrogen production occurs with glycoproteins, methane production will tend to fall so there may be some balance between hydrogen and methane production. There are endogenous and exogenous glycoproteins that are more likely to cause methane production. Those that tend to be carbohydrate poor are albumin and α-casein. Mucin normally tends to be carbohydrate rich.

In 1984 Piqué and colleagues showed that 91% of persons with untreated colon cancer excrete methane compared with 43% of healthy persons studied.[14] When the colon cancer was resected, the methane production fell to baseline levels. Interestingly, in a small group of patients with ulcerative colitis and colonic polyposi—"premalignant" conditions—75% had increased methane production. It is possible that colonic mucoprotein undergoes a change in the protein-to-carbohydrate ratio in the presence of colonic cancer. It has also been suggested that sugar-specific lectinlike mechanisms in the colon may change under the influence of local neoplasms. These affect the binding sites for colonic bacteria, and the change may favor colonization by methanogenic bacteria. Another possibility is that a slower transit time could favor the maintenance of colonization by methanogenic bacteria, as these are relatively slow-growing.

A higher fecal pH is present in populations that are at risk for colon cancer when compared with low-risk controls. Higher colonic pH may promote colon cancer by the formation of cocarcinogens due to bacterial degradation of bile acids or cholesterol, and there has been an association suggested of cholesterol ingestion with colonic cancer. There have been to date no prospective studies of the relationship between methane excretion and colon cancer, but this could conceivably be an important subject of future investigations.

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Epitomes
Important Advances in Clinical Medicine

Plastic Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in plastic surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in plastic surgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Plastic Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Craniofacial Surgery for Fractures

ONE of the major spin-offs of craniofacial surgery has been the development of new approaches for treating major fractures of the craniofacial skeleton. The use of these techniques has resulted in shorter hospital stays, a more stable reconstruction, fewer secondary steps in the final reconstruction and, perhaps most important, a much improved aesthetic result.

The primary approach is through a complete dissection of the involved areas, primarily through a bicoronial incision as in congenital craniofacial problems but using lacerations for access as well. Radiographic evaluation is of course helpful to define the areas but a complete computed tomographic scan will offer the most help in deciding where the fractures are located. It is especially important that the major facial supporting areas (orbital, nasofrontal, zygomatic and pterygomaxillary buttresses) be adequately exposed, including the mandible when necessary. All of the bones thus exposed are then in a position to be carefully wired together in their proper position.

Areas of severe bone comminution or avulsion are bone grafted in the primary stage using split skull, split rib and iliac crest grafts as necessary. As a result of the meticulous repair of the fractures and using the strong supporting bone grafts contoured to obtain a normal anatomy, a stable craniofacial skeleton can be recreated that will rarely require extraskeletal fixation. In selected cases, mini-bone plates can be very helpful for the lower face and mandible, but they should be avoided as much as possible in areas of thin subcutaneous tissue such as the lateral orbital rims. Intermaxillary fixation can often be avoided by using the techniques described. The soft-tissue support thus obtained is one of the major factors for the improved results in these cases. All of the techniques known in congenital craniofacial operations must be used as necessary to reconstruct these areas of major acute injury. The lacrimal system has required additional operations for obstruction in only 17% of patients with injury to the area.

Complications have been amazingly few considering the degree of injury being treated by such techniques. Infection of soft and hard tissues has been the primary problem but sequestrums have only occurred in a small percentage in the two series reported. All of the medical specialties involved with the head would participate in the care for these complex injuries.

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Facial Palsy

FACIAL NERVE PARALYSIS remains a difficult challenge for plastic and reconstructive surgeons. Vast strides in this field have been made in the past ten years due in no small part to the sophistication of microneurovascular techniques. Even patients with long-standing unilateral palsy may be able to regain symmetry in repose and in voluntary facial responses.

The myriad of techniques that have been advocated to deal with facial palsy attests to the fact that none have given perfect results. Following nerve transection, immediate or early direct repair or cable grafting provides the best results. If reinnervation from the proximal ipsilateral seventh nerve is not possible, another peripheral nerve must be provided. This, however, must be done within six to nine months of the injury to assure reinnervation by one year. After that time the muscles will have poor, if any, motion. The hypoglossal, spinal accessory and phrenic nerves have all been used, but most surgeons feel that the donor deficit produced is too great, the resultant facial movements gross, reeducated voluntary con-

trol is poor and the lack of emotional response makes these techniques less than ideal.

Microneurovascular surgery has spawned the most promising procedures. Cross-face microneural grafting to bring voluntary and involuntary input from the contralateral facial nerve can reanimate existing facial muscles if done within the first six months, or can be used to innervate free vascularized muscle transfers.

A two-stage procedure using a cross-facial-sural nerve graft from the normal to the abnormal side, followed in six to eight months by a free microneurovascular transfer of an appropriate muscle to the previously placed nerve graft and local vessels, has a high success rate—80% to 90%. Some reports have shown that almost half the patients regain some degree of independent control of the reanimated side. The ideal choice for motor unit is not resolved, but the gracilis (whole or in part) or the pectoralis minor produced the best results.

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Plastic Surgery for Nonwhites

THE DESIRE for aesthetic facial surgical procedures by nonwhite patients is increasing. Factors influencing this increase range from wishing to look less like a perceived ethnic prototype to the desire to resemble a star from the entertainment world.

By and large, Asian patients seek alteration of their eyelids and nose. Those of African and Malaysian background more often request a smaller nasal configuration.

The change in appearance from the hooded upper eyelid to a well-defined fold is often striking. Additionally, female patients report that applying eyelid makeup is easier. Methods vary but generally include surgical fixation of loose dermis to the underlying levator apparatus, establishing a new eyelid fold 6 to 9 mm superior to the eyelash margins.

Changes in nasal appearance usually involve elevating the nasal dorsum (profile), narrowing the alar bases (frontal) and providing a thinner, more defined nasal tip. Various alloplastic materials are currently in vogue for dorsal elevation, but these carry the risks of extrusion and displacement. Autogenous cartilage and bone grafts are more difficult to use but are more stable.

The methods used in nasal operations are not new, but are based on proven maneuvers—fitting the operation to the patient. As in all surgical procedures, careful patient selection, discussion of realistic expectations and skillful preoperative planning are essential.

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Keloid and Hypertrophic Scar

PENETRATING WOUNDS of the skin elicit a cascade of biologic and biochemical events including inflammation and a fibroproliferative response that results in the deposition of collagen, noncollagenous proteins and proteoglycans. Scar tissue is the end product. The quality of a scar is directly related to the efficiency of the regulation of collagen production during wound healing and, specifically, the balance between new collagen synthesis and collagen degradation during the later stages of the process. Under certain circumstances, the equilibrium between collagen anabolism and catabolism is imbalanced, resulting in overproduction of collagen. In the extreme, hypertrophic scar or keloid may result.

The biologic differences between hypertrophic scar and keloid have yet to be completely characterized. Traditionally, hypertrophic scar has been classified as exuberant scar production within the boundaries of the original wound. A scar that overgrows and spreads beyond the borders of the original wound is called a keloid.

Biochemical and morphologic studies of the fibrillar collagen ultrastructure, the nature of chemical cross-linking of collagen molecules and the cell types inhabiting keloid and hypertrophic scar were conducted by Knapp and co-workers. They found that collagen fibers and fiber bundles showed an inverse correlation between degree of organization and scar abnormality. In addition, the collagen in skin and mature scars was highly cross-linked while that of hypertrophic scar and keloid was progressively less so. Three types of fibroblast seemed to populate the scars, with their relative distribution varying among the scar types. They concluded that hypertrophic scar and keloid are not distinct pathologic processes but, instead, represent progressively more aberrant activity in the continuum of the wound healing response.

Other evidence suggests that keloid fibroblasts produce significantly more collagen per cell than do fibroblasts derived from normal skin and normal scar. It may be that keloid fibroblasts have lost the ability to respond to feedback inhibitory signals that normally regulate wound healing.

Among other elements in the production of hypertrophic scar and keloid, variation encountered in the microvascular regeneration of the wound bed with low oxygen and high carbon dioxide levels has been implicated as a factor in promoting excessive collagen deposition and scar. Others have shown that the extracellular matrix of the wound exerts a powerful effect on the biosynthetic activity of cells; a hypertrophic scar or keloid could develop as a result of abnormal turnover of the wound matrix during the healing process.

The traditional treatment of hypertrophic scar and keloid has involved five general approaches: surgical procedures, pressure, irradiation, corticosteroids and other drugs. Currently, intralesional injection of triamcinolone acetonide alone or in combination with surgical correction appears to be the most popular means of dealing with these scars. The precise mechanism by which corticosteroids influence an abnormal scar is not known. It may be that the steroids influence collagen synthesis in scars by enhancing catabolic aspects of

turnover. This may occur by removal of collagenase inhibitors or by promotion of the activity of collagenase present in the scar tissue.

Recently, the use of the neodymium-yttrium-aluminum-garnet laser has been explored in the treatment of keloid, and early clinical results are promising. The mechanism of action of laser irradiation to reduce keloid scarring appears to be associated with fibroblast inhibition. The influence of the laser on the integrity of fibrillar collagen also must not be discounted and is the subject of ongoing investigation.

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Immediate Breast Reconstruction

IMMEDIATE RECONSTRUCTION of the breast, done during the same operation as the ablative procedure, is being practiced more and more frequently. There are several factors responsible for this increase. Previously it was thought that immediate reconstruction might adversely affect the course of the disease following ablation. This concern now appears to be unwarranted. It was previously postulated that patients needed to have a period of mourning for the loss of a breast before reconstuction was attempted. This was based on the idea that acceptance of the reconstructed breast would be easier if a patient first went through this period of mourning. With the newer techniques now available, this is no longer necessary. Immediate reconstruction also eliminates the cost and anesthetic risk of a second procedure, a factor that has stimulated patient compliance. Current modern techniques of breast reconstruction have greatly improved the final cosmetic result and thus patient acceptance. Cooperation between plastic surgeon and general surgeon has led to improved preoperative markings and incision planning. This cooperation has helped to maintain medial breast skin whenever possible, thereby reducing medial scarring and making it increasingly easier to create unscarred visible cleavage. Similarly, correct planning is less likely to destroy the normal inframammary fold, a finding that has greatly improved the final cosmetic result.

Four methods are available today for immediate breast reconstruction. The method chosen is largely dictated by surgeon and patient preference and the amount of tissue available following the ablative operation.

- If the skin flaps left behind are thick enough, ample and viable, breast reconstruction may be easily achieved by the submuscular placement of an appropriately sized prosthesis. Nipple reconstruction and possibly a reconstructive procedure on the opposite breast to reduce any size discrepancies are evaluated after three months as a second procedure.
- If there is not enough skin available, though the existing flaps may be of adequate thickness, a two-stage procedure using a tissue expander may be used. The tissue expander is inserted and the wound allowed to heal. The expander is then gradually inflated percutaneously, over a period of weeks or months, until its volume is greater than that of the prosthesis to be inserted during the second procedure. Much like the expansion of the abdomen during pregnancy, this slow distension of the chest wall skin will allow sufficient laxity or stretch of the skin to accommodate a prosthesis used to reconstruct the missing breast. A tissue expander has now been developed that, once inflated to the appropriate size, is simply left in position as a prosthesis, eliminating the necessity for a second procedure other than that required for reconstruction of the nipple.
- Rapidly gaining far greater acceptance and popularity is the use of the transverse rectus abdominis myocutaneous (TRAM) flap, using the skin below or around the umbilicus to replace the breast tissue removed. An added bonus is the abdominal lipectomy or so-called tummy-tuck procedure done at the same time. The plastic surgeon can elevate the flap at the same time that the general surgeon does the ablative procedure. With this technique, the overall duration of the operation is greatly reduced. The natural feel and more natural appearance have made this method the choice of many.
- When conditions such as previous abdominal scarring or other factors make this impossible, surgeons may opt to use the latissimus dorsi myocutaneous flap with a prosthesis.

In summary, immediate breast reconstruction is rapidly gaining greater acceptance, and current techniques, including the use of the TRAM flap, have improved the feel and look of the final result while not adversely affecting the ablative procedure or postoperative management of patients.

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Immediate Treatment of Superficial Burns

LOCAL COOLING limits edema and prevents progressive thrombosis of the dermal capillaries that normally occur during the first few hours following burn injury. This can only be used either for burns of less than 5% of the body surface area or for selected areas, such as the face or hands. Applying cold (not freezing) water by immersion or covering with wet towels for 30 minutes has been beneficial even when started half an hour after the injury.

Following cooling, the injured part should be gently washed with soap and water to remove external dirt and contamination. Hair in and around the burn wound is shaved to prevent its entrapment in wound secretions. Broken blisters and loose skin are debrided by scissors excision. At this point the depth of the wound is assessed. The typical characteristics of the superficial partial thickness wound can be found: pain, blanching and capillary refill of the moist pink wound surface. Deeper and larger injuries will frequently require surgical consultation or referral to a burn center, but most smaller superficial injuries can be treated in an emergency department or a physician's office.

Antibiotics are not routinely prescribed to a healthy patient. Topical antibacterial creams, which require frequent dressing changes and cause pain and discomfort, are not

needed for the care of a small burn treated on an outpatient basis. The superficial injury will heal on its own if protected. This is most easily done by covering the cleaned wound with a single layer of coated fine mesh gauze (such as Xeroform, Adaptic, Vasoline and the like). This is covered with enough bulky absorbent material to collect wound secretions and prevent their accumulating at the wound surface or leaking through the dressing. A firm outer wrap is then applied to immobilize the injured part and prevent external trauma.

The dressing should be changed by a physician at 48 hours. The adherent inner gauze layer is not removed unless there are excessive secretions or evidence of infection. The absorbent layer is reapplied and the wound reexamined in another four to five days when the dressing is again changed. As the wound heals by reepithelialization, the gauze layer will spontaneously separate. With this method, most superficial burn wounds will heal in 10 to 14 days with only three to four dressing changes and minimal patient discomfort and inconvenience. In the few cases of wounds that are not healed by two to three weeks or that show signs of increased depth or infection, treatment can be switched to topical antibacterials and the patient referred for consultation.

Immediate cooling of the burn wound, followed by cleansing and protective dressings with infrequent changes, has proved to be a safe, cost-effective method for the outpatient treatment of burns.

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Surgical Procedures for Down's Syndrome Stigmata

SIGNIFICANT INTEREST in the surgical correction of the facial stigmata of the Down's syndrome followed the report of Lemperle and Radu in 1980. The operation uses standard well-established plastic surgical techniques individually tailored to a patient's particular needs. The most useful procedure is the reduction of an excessively large tongue to permit comfortable oral closure and eliminate an unsightly open-mouth position. Other recommended procedures include Z-plasties to eliminate the medial canthal webs, nasal augmentation, lateral canthoplasty, malar and chin augmentation and sharpening of the cheek and submandibular contours by excising the subcutaneous fat.

The indications for this surgical correction, however, remain controversial. Critics note that severely mentally impaired persons seem unaware of their appearance and thus are not benefited by cosmetic improvement. They point out that even if the Down's syndrome characteristics are eliminated and a patient is made physically attractive in repose, behavior and facial animation betray the presence of retardation. Proponents suggest that some children are afforded limited social opportunities because of their family's embarrassment. Thus, eliminating the facial stigmata of the Down's syndrome should improve the patients' and their families' quality of life by enhancing social interaction. Unfortunately, there are no well-done studies that support this impression. Also, many families grasp at any suggested treatment to leave no stone unturned for their loved one. In their zeal to do everything possible, parents may lose their objectivity and become easily persuaded to subject their child to an "Emperor's clothes" operation.

Operative intervention must be tailored to the entire sociopsychological milieu of the patient, the family and their interactional environment. The decision for surgical correction must be made by an informed and well-counseled family. Sometimes attempts at attitudinal change may be more traumatic than an operation. Such cases should be recognized by the treatment team who should not be judgmental and deny or discourage a surgical procedure because of their personal bias.

Simple reduction of a very large tongue can benefit even a profoundly retarded person, both by improving the airway and by eliminating a feature that can be a severe social impediment even in sheltered environments. For those few patients with the Down's syndrome who function at a relatively high intellectual level, the benefits of an operation are less controversial. Such patients will often have enough insight to make their decision, and usually actively solicit treatment.

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Face-lift Techniques Today

FOR THE BEST results, it is necessary to define the goal of an aesthetic facial operation. Most patients seeking such improvement of the entire face and neck wish to have their good looks restored, to appear as alert and youthful as possible or to improve features that have never been pleasing. Almost all patients would like the detectability of the scars minimized and the secondary problems, such as abnormal hair patterns following the surgical procedure, eliminated or minimized. The attainment of perfection is not possible; nevertheless, surgeons should use all of their diagnostic and surgical skills to try to reach this goal.

A precise anatomic diagnosis of the cause of facial problems is essential to plan the use of the structures to achieve maximum improvement. A detailed study of the contours and proportions of the forehead, cheeks, eyelids, eyebrows, lips, chin, neck and ears is necessary for planning the location of the incisions and the new position of the skin, subcutaneous tissue, fat and deep structures of the face. For example, if more than 2.5 cm of skin is to be discarded in the direction of the temporal hair, most patients will have a more pleasing appearance, without abnormal elevation of the hair, if the incision is placed to follow the hairline in the temporal area and to allow the hair in the sideburn area to be lower than the top of the ear. Creating a distance between the lateral canthus of the eyelids and the temporal hair of greater than 4 cm gives

an older appearance, and less than 4 cm a younger appearance. In addition, the portion of the ear skin between the earlobe and the tragus should be preserved if the incision is made along the edge of the tragus, as the appearance of the tragus after the procedure is nearly as important as the appearance of the nasal tip. The tragus size and contour should be in keeping with the size of the ear of each patient, not a standard height or width. The location of the incision in the occipital area will determine whether a female patient will be able to wear her hair pulled backward in a bun or pulled upward, or will be limited to a hairstyle that would hide a "step deformity" in the occipital area.

Improving the appearance of the forehead, face and neck has been made possible by techniques that correct problems of the skin, fat, muscles and superficial supporting fascia. Techniques previously used, which relied on skin traction alone to compress or elevate fat and sagging muscles, frequently resulted in only a moderate improvement of short duration, and often the tension would result in wide or depressed scars. The many details of a handsome or a beautiful face that together create the appearance of youth or beauty require careful preoperative planning. The changes in facial contour that occur with the aging process are related to changes in the platysma muscle, superficial musculoaponeurotic system muscles of expression, subcutaneous tissues and skin. Changes of the hair contour and the eyebrow position all take part in the appearance of annoyance, sadness, tiredness or alertness, youth and vitality.

The attention to details of the anatomic diagnosis can be followed by an exact and appropriate plan for skillfully and safely doing the surgical correction. The placement of skin incisions to minimize scar detectability and to avoid abnormalities of hair pattern is very important. These postoperative abnormal hair patterns may interfere with work and recreational activities. The superficial musculoaponeurotic muscles with their skin attachments to the nasolabial fold, upper lip, lower lip, chin and submental area require precise shifting to produce the maximum support to these areas and to improve the folds of the platysma muscle in the submental area. This shift in an upward and lateral direction not only produces an improvement at the time of the operation, but decreases the tension on the scar at the temporal area. Consequently, the possibility of reducing scar tension is better when the deep layer of the superficial musculoaponeurotic system and platysma muscle are used for support.

There is no standard "cookbook" operation that will deliver the best results for each face and neck problem. The best result is accomplished by many modifications of several procedures, designed specifically for each patient's particular problem.

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Editorials

Seminars in Health Care Delivery

At a recent Annual Meeting of the Editorial Board it was suggested that in view of the growing importance of socioeconomics in the delivery of health care, the journal should begin to offer more on this subject for the information and perusal of its more than 54,000 readers. In response to this suggestion a series of Seminars in Health Care Delivery was planned.

The editors were fortunate indeed when Steven A. Schroeder, MD, agreed to be the editor for this series. Dr Schroeder not only is a distinguished clinician, a leading teacher of primary care internal medicine and consultant to a number of private foundations and government agencies, but he also is widely known for his scholarship and publications in many aspects of health care delivery. Among his many responsibilities, he currently serves as a member of the US Prospective Payment Assessment Commission and chairman of its Data Development Committee.

The journal welcomes Dr Schroeder and looks forward to the series of Seminars in Health Care Delivery that is being developed under his leadership, the first of which appears in this issue.

MSMW

New Roles for Activated Charcoal

Derlet and Albertson in their excellent review entitled "Activated Charcoal—Past, Present and Future" in this edition of the journal have provided a scholarly summary of the development, current uses and new roles of oral activated charcoal in the treatment of poisoned patients. They not only focus on the use of activated charcoal as an adsorbent of many common poisons and drugs to prevent their absorption from the gut but also review the role of multiple doses of oral charcoal in increasing the clearance of certain substances from the body (gastrointestinal dialysis).

As pointed out by the authors, a new form of superactivated charcoal is available and has been recently released for clinical use in the United States.[1] This charcoal (Super-Char) has a surface area of 2,500 to 3,500 m^2 per gram, or approximately three times as much as the older forms of activated charcoal.[1] This substance, as expected, is approximately three times as effective (on a weight basis) in both adsorbing drugs and in increasing the clearance of drugs from the body. The advantage of superactivated charcoal is that only approximately a third the amount of standard charcoal is necessary to decrease absorption or increase clearance of intoxicants comparably. There are some patients who are unable to drink 60 grams of charcoal but who can drink 20 grams. Thus, superactivated charcoal is an important advance in charcoal preparations and its use has been adopted in many institutions in the United States.

Activated charcoal use is not without limitations. Many drugs and intoxicants are not well adsorbed by activated charcoal, as pointed out by Derlet and Albertson. These include lithium, methanol and ethylene glycol. Moreover, there are other drugs that, although they are adsorbed by activated charcoal, their clearance is not accelerated by multiple doses of oral charcoal.[1] For example, in one carefully done study with intravenously given imipramine hydrochloride (a tricyclic antidepressant), the imipramine clearance in subjects receiving multiple doses of activated charcoal was no greater than in those who received no charcoal.[2] Similarly, digoxin clearance is only increased by approximately 30% with multiple doses of oral activated charcoal in normal subjects.[1] It is experimentally clear, however, that many drugs, including salicylates, barbiturates, carbamazepine, dapsone, digitoxin, nadolol, theophylline and the pesticide chlordecone, have greatly increased clearances by multiple doses of oral activated charcoal.[1]

In previous publications, we have proposed a simple pharmacokinetic model to explain the ability or lack of ability of multiple doses of activated charcoal to increase the clearance of drugs and poisons from the body.[1,3] The total body clearance (Cl_T) of a drug or poison is the summation of clearances by all methods of removal from the body. Thus,

$$Cl_T = Cl_K + Cl_L + Cl_{GI},$$

where the subscripts K, L and GI refer to elimination by the kidney, metabolism and excretion by the liver and removal by charcoal through the gastrointestinal tract, respectively. Therefore, the significance of the contribution of charcoal on Cl_{GI} to Cl_T will depend on the magnitudes of Cl_{GI} relative to Cl_K and Cl_L. We have shown this by comparing the effect of charcoal on the clearance of theophylline as a model drug in normal subjects and patients with hepatic cirrhosis. As the endogenous theophylline clearance (Cl_L and Cl_K, due to hepatic and renal elimination) decreased in normal subjects and in patients with hepatic dysfunction, the effect of charcoal (Cl_{GI}) on theophylline clearance (Cl_T) increased.[1,3] Therefore, even if endogenous clearance declines to zero, the total clearance (Cl_T) will never be less than the Cl_{GI} achieved by charcoal in the gut.

The rate of removal of a drug or poison by charcoal in the gut is strongly influenced by the apparent volume of distribution (V) of the drug or poison.[1]

$$\text{Rate of removal by charcoal} = Cl_{GI} \times C$$
$$= Cl_{GI} \times A/V,$$

where C is the concentration of drug or poison in the plasma and A is the amount of drug or poison in the body. Therefore, for any given amount of drug or poison (A) and clearance rate (Cl_{GI}), the rate of removal by charcoal in the gut is inversely related to the volume of distribution. That is, drugs with large volumes of distribution will not be effectively removed by oral activated charcoal. An example of such a drug is imipramine.

We can make some general predictions as to which drugs and poisons may or may not be effectively removed from the body by multiple doses of oral activated charcoal.[1] It would be expected that drugs or poisons that can easily diffuse across the gut membrane and have small volumes of distribution (less than 1 liter per kilogram of body weight) would be effectively

removed. Theophylline, phenobarbital and digitoxin generally fit these criteria. Conversely, digoxin and tricyclic antidepressants such as imipramine have large volumes of distribution and show limited removal by charcoal. Overall, the principles that govern the ability of oral activated charcoal to increase the clearance of drugs and poisons from the body are analogous to the principles that govern the effectiveness of hemodialysis and hemoperfusion for removing drugs and poisons. Major exceptions to this generalization are drugs and poisons that are not adsorbed by charcoal or that do not enter the gut from the blood. For example, we would not expect aminoglycoside antibiotics to be effectively removed since they do not cross the gut membrane, as evidenced by lack of absorption when they are administered orally.

Of course, this model for increasing drug clearance with activated charcoal assumes that adequate charcoal is given to fill the gut lumen.[1] This is done generally by giving doses of approximately 20 grams of superactivated charcoal every two hours for maximum effect.[1] Activated charcoal can also be used as an adsorbent in hemoperfusion systems to increase the clearance of drugs, but this is beyond the scope of this editorial.[4]

In summary, there is no question that charcoal given orally, especially superactivated charcoal, can decrease the absorbance of many drugs from the gut and, in many cases, increase the clearance of drugs from the body, sometimes substantially. Thus, there is no doubt about the pharmacokinetic efficacy of charcoal as both an adsorbent and a substance to increase clearance. What has never been clearly established, however, is that these impressive pharmacokinetic properties of charcoal are, in fact, related to better patient outcome.[5] Derlet and Albertson in their review discuss this important point and we would reemphasize this question. First principles in pharmacology and medicine would strongly suggest, that, if less drug or intoxicant is absorbed, the patient will have less of a toxic reaction; or, if the drug or intoxicant is more rapidly removed, the patient will suffer less adverse effects. This should result in less morbidity—that is, shorter times in intensive care units. These assumptions, however, remain to be established conclusively in controlled clinical trials.

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Need Kidneys Fail?

THE RATE OF PROGRESSION to end-stage renal failure is not influenced solely by the extent and severity of the primary renal insult. Amplifiers of risk include systemic hypertension, urinary tract infection or obstruction and intrarenal deposition of calcium and urate salts. Often, however, despite control of these risk factors, mild but permanent kidney injury eventually results in progressive deterioration of renal function. These observations suggest that reduction of the number of functioning nephrons beyond a certain point ultimately leads to failure of the remaining nephron units. Investigation into the mechanism(s) responsible for this process in animals has shown that progressive loss of these residual nephrons is a predictable consequence of the glomerular hemodynamic response to renal injury and, in particular, to the adaptive increase in glomerular capillary hydraulic pressure that regularly follows a decline in the number of functioning nephrons.[1] Some of the evidence upon which our hypothesis is built is reviewed by Avasthi elsewhere in this issue.

A pattern of progressive azotemia, proteinuria and glomerular sclerosis similar to that found in animals after partial renal ablation is also observed in clinical settings following a circumscribed renal injury. These include bilateral renal cortical necrosis and vesicoureteral reflux. Likewise, acute poststreptococcal glomerulonephritis and the various forms of lupus nephritis occasionally progress to chronic renal failure in the absence of continued immunologic injury. Hemodynamic factors may also explain the observation that pregnancy, with its attendant increments in glomerular filtration rate and renal blood flow, frequently accelerates a loss of renal function in women with preexisting kidney disease.

These observations therefore urge the answering of a number of clinical questions. First, what degree of renal mass reduction in humans results in progressive glomerular disease? Some information in this regard is available from studying cases of the congenital renal disease, oligomeganephronia, a condition characterized by a reduction in nephron number to approximately 20% of the normal complement and by pronounced hypertrophy of those nephrons present. Hyperfiltration per nephron in this disorder initially maintains the total glomerular filtration rate at an acceptable level, but by adolescence children with this condition typically have progressive proteinuria, glomerular sclerosis and renal failure. More common is unilateral renal agenesis, where glomerular hyperfiltration in a solitary kidney maintains renal function at near-normal levels during childhood, only to eventuate in the development of renal failure in early adult life in some affected persons. It would thus appear that a reduction of renal mass by half or more during very early life imposes a risk, as yet unquantified, for subsequent hemodynamically mediated overt renal injury.

A second important question is whether increased glomerular capillary pressures can initiate progressive glomerular disease even when the number of functioning nephrons is normal. We have suggested that the protein-rich diet characteristic of modern Western society may induce chronic renal hyperperfusion and hyperfiltration, thereby contributing to the glomerulosclerosis seen with aging.[1] The recent observation that clinically overt proteinuria and renal insufficiency are more likely to develop in those patients with type I diabetes who have substantial hyperfiltration early in the course of their disease than in those patients with lesser initial degrees of hyperfiltration also supports an affirmative answer to this question.[2] Additional support is found in sickle cell anemia, which, although classically associated with papillary

ischemia, is also characterized by greatly elevated renal blood flow and filtration rates during the first decade of life, followed by a gradual loss of renal function and widespread glomerular sclerosis by the third decade.[3]

Standard treatment modalities for chronic renal insufficiency do little to impede this relentless hemodynamic process. But several strategies aimed at interrupting the underlying hemodynamic events, or subsequent steps in the injury process, might serve to forestall the otherwise predictable progression to end-stage renal disease. Restriction of dietary protein has been shown to substantially slow and perhaps even halt the progression of many forms of chronic renal disease in humans.[4,5] Evidence suggesting that treatment of hypertension also slows this progression has likewise been reported, including the recent demonstration in diabetic animals that antihypertensive therapy with a potent angiotensin I-converting enzyme inhibitor provides substantial protection against glomerular injury even when the drug is administered to animals that do not display systemic hypertension.[6] It should be recognized, however, that not all antihypertensive regimens successful in reducing systemic arterial pressure result in an equivalent lowering of glomerular capillary pressure,[7] and it therefore becomes of paramount importance in treating systemic hypertension in patients with underlying renal vasodilatation to construct a medical regimen specifically designed to alleviate intraglomerular hypertension. At our present state of knowledge, this challenge seems best met by the use of converting enzyme inhibitors. Strict metabolic control in patients with diabetes, achieved by continuous insulin infusion or other means and instituted early in the disease's course, could likewise prove effective in preventing glomerulopathy. Such tight control, however, is difficult to achieve widely and therefore renders an aggressive lowering of blood pressure and avoidance of excessive dietary protein mandatory adjuncts in the management of these patients.

A final question that derives from these earlier considerations concerns the appropriate time for initiating potentially beneficial therapy. With a 50% reduction in the glomerular filtration rate, the serum creatinine concentration increases only slightly, but even this slight increment reflects a tremendous insult to the overall nephron population. It is therefore essential that institution of therapy for patients at risk for hemodynamically mediated renal injury not await documentation of more severe functional compromise, but should precede these impairments and thereby delay if not avert them.

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Case Reports

Mebendazole and *Ascaris* Migration

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Ascaris migration from the nose and mouth during mebendazole treatment was reported in Guatemalan children with heavy *Ascaris lumbricoides* infections.[1] A review of mebendazole therapy[2] indicated a similar experience in the Philippines and Indonesia, but the authors stated that "researchers in other parts of the world have not experienced this problem."

We report the cases of three children who had *Ascaris* migration from the nose or mouth after receiving mebendazole.

Reports of Cases

Case 1

The patient, a 2½-year-old Filipino girl, had watery diarrhea. She had a history of eating dirt in the Philippines. On physical examination no abnormalities were noted. Her hemoglobin was 11.7 grams per dl; the leukocyte count was 12,700 per μl with 35% polymorphonuclear leukocytes, 4% bands and 14% eosinophils. *Ascaris* and *Trichuris* ova were seen in the stool. Mebendazole, 100 mg, was given twice a day for three days. During treatment, four adult *A lumbricoides* passed per rectum and one adult *Ascaris* emerged per os.

Case 2

The patient, an 11-month-old Filipino girl, had several threadlike white worms coming from the anus at night. Mebendazole, 100 mg, was given by mouth with a clinical diagnosis of pinworms. An adult *Ascaris* came from the nose three days after the administration of mebendazole when the child was otherwise well. The family had moved from the Philippines three months before her clinic visit.

Case 3

A 5-year-old Filipino-American boy was seen in the pediatric clinic one day after his 18-month-old brother spontaneously passed an adult *Ascaris* per rectum. Physical examination showed no abnormalities. The leukocyte count was 12,400 per μl with 43% polymorphonuclear leukocytes, 2% bands and 9% eosinophils. Mebendazole, 100 mg, was given twice a day for three days after *Ascaris* and *Trichuris* ova were seen in two stool specimens. Three adult *A lumbricoides* came from his mouth during the three days after beginning the mebendazole regimen, and four or five adult *Ascaris* were passed per rectum. The family had moved from the Philippines one month before the clinic visit.

Discussion

Ascariasis and trichuriasis are the most prevalent intestinal helminthiases, infecting 1 to 2 billion people worldwide.[3] Drugs available to treat *Ascaris* infections include pyrantel pamoate, piperazine citrate and mebendazole. Mebendazole is also the treatment of choice for trichuriasis.[4]

Mebendazole causes cytoplasmic microtubular degeneration and death of intestinal-dwelling adult *Ascaris* by selectively and irreversibly blocking their glucose uptake without affecting blood glucose levels in the host, including humans.[2] In clinical trials with mebendazole, cure rates and percent reduction in *Ascaris* egg output of nearly 100% have been reported.[4]

Adverse effects in patients treated with mebendazole have been infrequent. The first study in humans by Brugmans and co-workers reported no adverse effects in 702 patients.[5] Transient symptoms of diarrhea and abdominal pain have occurred in children with heavy parasitism.[6]

Migration of *Ascaris* from the nose or mouth following mebendazole treatment has been reported previously from Guatemala,[1] Costa Rica,[6] Indonesia,[7] Bangladesh[8] and the Philippines.[9] Only children with heavy worm burdens (100 to 200 *Ascaris* passed in the stools after treatment) experienced erratic migration in Guatemala, but both 2% to 4% of children in the Philippines[9] and 1% to 2% of people in Indonesia[10] treated for ascariasis with mebendazole alone have noted erratic migration. Combination therapy with mebendazole, 150 mg, and pyrantel base, 34 mg, had the efficacy of mebendazole but did not cause erratic migration of *A lumbricoides* in more than 3,000 treated patients.[10]

Our cases were in children with light worm burdens (ten or fewer *Ascaris* in the stools after treatment) who had recently come to the United States from the Philippines. Other methods to semiquantitate worm burdens in our cases, such as determining the number of eggs per gram of feces, were not done.

Physicians have been advised that intestinal parasitic infections have a high prevalence among mainland Indochinese refugees,[11,12] but similar advice for persons coming from the Philippines has not been well emphasized in the recent American literature. In the 24 months following our first case, 21 children from 16 families had a diagnosis of *Ascaris* infections. Of the 21 cases, 19 came from the Philippines.

Spontaneous oral passage of *Ascaris* occurred in 3.3% of

(Brawley RL, Van Meter Q: Mebendazole and *Ascaris* migration. West J Med 1986 Oct; 145:514-515)

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580 cases of ascariasis in Poland.[13] In 13 of our 21 patients, we had data about the passage of *Ascaris* after mebendazole treatment; passage from the nose or mouth occurred in 3/13 patients. The reasons for the erratic passage of *Ascaris* following mebendazole treatment in our patients were unclear.

Physicians using mebendazole to treat ascariasis should inform patients and their families about the possibility of aberrant migration of *A lumbricoides* from the nose or mouth. This advice may be especially prudent for persons from Indonesia and the Philippines because aberrant migration after using mebendazole alone has been noted most often there.

Further studies of combination chemotherapy[10] should be conducted to confirm that aberrant *Ascaris* migration does not occur when the two drugs are used, confirm the therapeutic efficacy of the combined drugs for hookworm, ascariasis and trichuriasis and determine the safety of the combined drugs.

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Hot Flashes in Men With Testicular Insufficiency

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ALTHOUGH HOT FLASHES commonly accompany menopause in women, such symptoms are far less common in men.[1] Hot flashes in both men and women are characterized by an increase in peripheral blood flow and pulse[2] which typically causes reddening of the face, neck and trunk, sweating and occasionally syncope. Hot flashes in men may occur following orchiectomy or abrupt testicular failure such as that due to arterial compromise following multiple herniorrhaphies.[1] It is important for physicians to recognize this condition in men because hot flashes can be disabling and, on occasion, mimic cardiovascular disease. The following report illustrates many of the salient features of hot flashes in men.

(Norcross WA, Schmidt JD: Hot flashes in men with testicular insufficiency. West J Med 1986 Oct; 145:515-516)

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Report of a Case

A 79-year-old man was referred by the Urology Service, which was following him for prostatic adenocarcinoma, to the Family Medical Center for general medical care. One month later, severe right hip and low back pain developed. Findings on a bone scan and plain films of the right hip and lumbosacral spine suggested metastatic lesions of the T-9 and L-5 vertebrae. A bilateral orchiectomy was done. Within the first three weeks postoperatively, he was nearly free of pain but noted episodes of hot flashes and sweats occurring several times a day and generally lasting for one to three minutes. Although bothersome, the patient regarded them as tolerable. One year postoperatively, the patient had a severe hot flash that progressed to syncope. Evaluation in the Coronary Care Unit of the University of California, San Diego, Medical Center failed to reveal a cause for the hot flash. Thereafter, the hot flashes seemed to increase in intensity, though not in frequency. Therapy was begun with a preparation of phenobarbital (20.0 mg), ergotamine tartrate (0.3 mg) and levorotatory alkaloids of belladonna as malates (0.1 mg) (Bellergal; Dorsey Pharmaceuticals, Division of Sandoz, Inc, East Hanover, New Jersey) with fair results. Both the intensity and the frequency of hot flashes diminished. Eight months later the Bellergal therapy was discontinued and a regimen of diethylstilbestrol, 0.5 mg twice a day, was instituted in an effort to improve control of his hot flashes. At the time of this writing, the patient's hot flashes have reverted to the frequency and severity experienced before therapy, though he has had no syncopal episodes.

Discussion

Vasomotor symptoms seem to be related to the period of time over which gonadal function wanes. Whereas female gonadal function diminishes rather abruptly during the perimenopausal period, male gonadal function is commonly much more gradual, with significant testosterone production often maintained into the seventh and eighth decades of life.[3] Additionally, most recent reports of hot flashes in men have occurred in patients having lost gonadal function abruptly due to orchiectomy for prostatic or testicular cancer, or from damage to the spermatic cord following multiple herniorrhaphies.[1,2,4]

The cause of hot flashes in both women and men is unclear. Although sex hormone replacement effectively treats hot flashes in both sexes, the absence of estrogen or testosterone alone cannot fully explain the vasomotor symptoms. Women with hypoestrogenemia due to ovarian agenesis and prepubertal women do not have hot flashes.[4,5] Neither can elevated levels of gonadotropins completely explain the vasomotor phenomena since hot flashes do not occur in patients with Klinefelter's syndrome or gonadal dysgenesis, conditions in which gonadotropin levels are almost invariably high.

In rat brains, estrogens have been shown to have a modulatory effect on catecholaminergic pathways.[6,7] Estrogen de-

ficiency appears to increase the ratio of norepinephrine to dopamine in the rat central nervous system, an effect that is reversed following estrogen supplementation.[6,7] Additionally, the use of clonidine, a central nervous system α-adrenergic agonist, has been shown to be quite effective in suppressing the hot flashes of both men and women.[2,8]

Further evidence for a central mechanism of hot flashes was provided by the discovery of "pulses" of luteinizing hormone secretion during menopausal hot flashes.[9] In female rats, the neurons responsible for the secretion of luteinizing hormone-releasing factor are in proximity to the thermoregulatory centers of the anterior hypothalamus and appear to be regulated by estradiol.[10] Also, administering a gonadotropin-releasing hormone agonist to normal men has been shown to cause hot flashes in some, but not all, subjects.[11] (Now that leuprolide, a gonadotropin-releasing hormone analogue, has been shown to be effective in the treatment of metastatic prostate cancer,[12] physicians, particularly urologists, might expect to see hot flashes in men more commonly.) Although the lutcinizing hormone level increases with hot flashes, it is difficult to attribute a causative role to it alone because hot flashes may occur following surgical removal of the pituitary.[13]

Although the etiology of hot flashes remains elusive, the clinical manifestations are compatible with a "downshifting" of the thermoregulatory centers,[14] and there is evidence for anatomic and neuroendocrine linkages between these centers and that of luteinizing hormone-releasing factor. Available data suggest that the site of dysfunction resulting in hot flashes is the anterior hypothalamus, although the precise mechanism remains to be elucidated.

The therapy for hot flashes in men must be considered in light of the underlying disease process and the wishes of the patient. When no contraindication exists, testosterone replacement effectively treats the vasomotor symptoms as well as the problems of diminished libido and sexual dysfunction.[1] When a contraindication to testosterone exists, such as in our patient, several choices are possible. The use of estrogens, though highly effective for controlling vasomotor symptoms, must be weighed against the risk of heart disease. Clonidine has been used with success for both men and women.[2,8] Our patient obtained significant relief from a preparation of phenobarbital, ergotamine and belladonna, but to date has noted no improvement with the use of diethylstilbestrol. Although placebo alone has been shown to diminish the frequency of hot flashes in women,[8] we conjecture that the preparation of phenobarbital, ergotamine and belladonna may well have a pharmacologic basis for having a salutary effect on hot flashes. Though no direct supporting evidence exists, a low dose of ergotamine may be expected to inhibit peripheral vasodilation, and belladonna may inhibit the sweating associated with hot flashes. Recently, the gonadotropin inhibitor, cyproterone acetate, has been found in a double-blind crossover study to be quite effective in diminishing the frequency of hot flashes in men who have had bilateral orchiectomies.[15]

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Pulmonary Dirofilariasis in Humans—Pneumonitis That Evolved to a Lung Nodule

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SOLITARY LUNG NODULES in humans from *Dirofilaria immitis* are rarely observed in the western United States.[1] Most cases are reported from the southeastern United States, an endemic region with a high prevalence rate of dirofilariasis among the canine population.[2-4] Ciferri reported the first documented case of human pulmonary dirofilariasis acquired in northern California and reviewed the epidemiologic factors that allow transmission of this zoonosis to humans.[1] We report an additional case of a patient from California who presented with acute pneumonitis that evolved over three months to a solitary lung nodule, proved at thoracotomy to be due to *D immitis*. Canine heartworm infection and the mosquito vectors necessary for transmission of microfilariae from dogs to humans are present in southern California.[5-7] We review the patient's travel history and the local factors that resulted in his infection, including canine surveys and mosquito exposure. The roentgenographic evolution and the immunology of dirofilarial lung nodules are discussed.

Report of a Case

A 50-year-old man, an Air Force pilot from Riverside County, California, presented with nonproductive cough,

(Smith LS, Schillaci RF: Pulmonary dirofilariasis in humans—Pneumonitis that evolved to a lung nodule. West J Med 1986 Oct; 145:516-519)

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low-grade fever and left pleuritic chest pain. A chest roentgenogram showed a patchy infiltrate in the peripheral left lower lung field (Figure 1). He was treated as an outpatient with administration of antibiotics by mouth, and all symptoms resolved within ten days. A repeat film a month later showed a denser infiltrate that had decreased in size. Another film two months after the initial presentation showed a well-circumscribed 2- by 2-cm nodule in the left lower lung field in the region of the previous infiltrate (Figure 2).

He was referred to the Pulmonary Division of the Naval Hospital, San Diego, for further evaluation.

The patient had a 20-pack-year smoking history, but he had not smoked for ten years. On physical examination no abnormalities were noted. Skin tests for coccidioidin, spherulin, histoplasmin and tuberculin were all negative. An eosinophil count was normal and coccidioidal serologic tests were negative. Conventional tomography of the lung nodule showed no cavitation or calcium; borders of the nodule were smooth, and the lateral edge was contiguous with pleural surface. A computed tomographic scan confirmed the conventional tomographic findings; no other nodules were found. Bronchoscopy showed normal anatomy, and washings in the region of the nodule yielded normal cytologic findings and negative cultures for fungal and mycobacterial species. A gallium scan did not show uptake in the nodule.

Because of the patient's age, smoking history and his concern about the nodule, a left thoracotomy and a wedge resection were done. On microscopic examination there was a discrete caseous granuloma. Lymphocytes, plasma cells and an occasional multinucleated Langerhans-type giant cell formed a mantle of chronic inflammatory cells, including an occasional lymphoid follicle. The necrotic remains of a coiled roundworm partially replaced by dystrophic calcification was seen centrally. The anatomic structure was focally preserved and it showed the characteristic bilateral, internal, longitudinal ridges and cross striations of the cuticle of *D immitis* (Figure 3). Also noted were three centrally located tubes that were the alimentary tract and the double uterus of the immature female worm. Additional history revealed that the patient had traveled briefly to North Carolina nine months before his pneumonitis developed, and dogs belonging to relatives with whom he resided had been treated for heartworms.

Discussion

Few cases in the literature have shown the clinical and roentgenographic natural history of human pulmonary dirofilariasis, with progression from pneumonitis to a solitary lung nodule. Feld described a case of a patient with an ill-defined infiltrative lesion in the lung associated with cough and dyspnea; three weeks later the lesion appeared more nodular, and resection showed *D immitis* in an area of infarction.[8] Chesney and associates resected a lung nodule that had increased in size over 18 months, and they found *D immitis* surrounded by a hypersensitivity reaction. They considered centrifugal leak of

Figure 1.—Chest roentgenogram coned to the left lower lung field shows a patchy infiltrate.

Figure 2.—Chest roentenogram taken three months after the initial film shows a 2- by 2-cm noncalcified nodule in the region of the previous infiltrate.

antigen with local immunologic reaction to have been responsible for the increased size noted on chest roentgenogram.[4] A dirofilarial nodule found in a lobe of lung affected by pneumonia 11 months previously was described by Navarrette.[9] The remainder of the cases reviewed in the literature report a coin lesion as the initial roentgenographic manifestation of human dirofilarial infection.[2,10,11] A physician in southern California, confronted with a patient in whom a solitary, noncalcified pulmonary nodule develops in the region of a prior pneumonitis, will consider coccidioidomycosis the most likely diagnosis. In our patient, negative coccidioidal skin tests and serologic study, a history of tobacco use and his interest in a definite diagnosis led to thoracotomy, during which a lung nodule from *D immitis* was resected. A needle aspiration was not attempted. Hawkins and co-workers reported a case of pulmonary dirofilariasis diagnosed by needle aspiration.[12] Four additional patients with dirofilarial nodules had nondiagnostic transthoracic needle aspirations.[13]

Endemic areas within the continental United States that are prevalent for canine infestation by dog heartworm are the Atlantic and Gulf Coasts and the Mississippi River Valley.[9] Human cases are found predominantly in these areas. A single case of human dirofilarial infection acquired in northern California has been described by Ciferri, who reviewed the epidemiologic factors necessary for transmission of this zoonosis to humans.[1] For humans to be infected, they must be bitten by a species of mosquito that is capable of supporting the development of dirofilarial larvae to the infective stage, and the infection must be prevalent in the local canine population. These conditions exist in Riverside County where the patient lived for the year preceding his infection. Canine surveys have documented the presence of *D immitis* in dogs in Riverside County,[5] and mosquito vectors capable of transmitting *D immitis* are found in southern California.[6,7] Corselli and Platzer also noted in their review of canine heartworm infection in southern California that temperatures in Riverside County rarely drop below 22°C (72°F) during the spring and summer months, so that development of *D immitis* in its arthropod host could easily be sustained.[5] Our patient was not aware of a significant mosquito population around his home; he owned two dogs that were healthy, but they were not tested for occult dirofilariasis. He traveled to North Carolina nine months before his lung nodule became apparent and may have acquired *D immitis* during his two-week stay in that area, where canine heartworm infection is prevalent. Dogs belonging to relatives with whom he resided were treated for *D immitis*. However, conditions exist in Riverside County that allow transmission to humans, and we cannot exclude the possibility that he acquired his infection in California.

Figure 3.—Cross-section of the pulmonary artery and surrounding granuloma contains a partially necrotic roundworm with dystrophic calcification and the characteristic bilateral longitudinal ridges (original magnification × 45).

The life cycle in the secondary human host starts with injection of microfilariae by a mosquito into the integument. They then migrate to the right side of the heart, where they reach maturity in six months.[1] In humans, the worm dies before it reaches sexual maturity and is embolized to the lungs. The dead worm lodges in the pulmonary artery, resulting initially in an infarct, with subsequent development of an immunologic response. In our patient, the initial appearance of pneumonitis with symptoms of pleuritic pain could be explained by end-artery embolism and infarction; the lesion was not wedge-shaped, however, and was more suggestive of a local inflammatory response. The nodule may develop from a "spherical infarct," but most reviewers emphasize the histologic demonstration of a granuloma. Centrifugal diffusion of antigen is probably responsible for an encircling immunologic response that results in the typical coin lesion seen on chest roentgenogram.[2,4,14-16]

The presence of microfilariae in a blood specimen from a dog allows the rapid diagnosis of dirofilariasis.[17] Occasionally microfilariae will be absent in dogs who have adult worms, a state known as "occult dirofilariasis," reflecting the presence of antimicrofilarial antibodies.[18-20] The immunologic response to *D immitis* has been well studied in the canine population. Humans are an infrequent host as the worm dies in humans before it produces microfilariae.[9] This suggests an immune-mediated death, but the serologic and cell-mediated immune responses in humans are not well understood. Conclusive prethoracotomy diagnosis is hampered by the lack of predictable serologic and skin test responses, cross-reaction of filarial antigens and a low incidence of dirofilarial-related lung nodules.[21]

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Comments on the Forum

TO THE EDITOR: Please accept my sincere congratulations to *The Western Journal of Medicine* for its wonderful opening series of essays in the forum on "The Aim of American Medicine Within the Constraints of Today's Society."[1] This sort of leadership in airing the important views of nondoctors, as well as doctors, is long overdue in all of our journals. Physicians are slow to realize that we may not be the "judges in our own cause."

I believe this kind of openness and dialogue with all segments of society is the only way to a sane system of health care.

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REFERENCE

1. The aim of American medicine within the constraints of today's society—A Forum. West J Med 1986 Aug; 145:181-191

EDITOR'S NOTE:

Readers are invited to contribute their views to this forum, which continues elsewhere in this issue.

MSMW

Recommendation for a Change in Certificates of Death

TO THE EDITOR: Unfortunately, deaths related to pregnancy still occur and remain underreported.

Coccidioidomycosis in pregnancy remains the commonest single cause of maternal mortality at Kern Medical Center, Bakersfield, California. A review of medical records showed that deaths in young women with disseminated cocci and pregnancy had not been included in the maternal death records of the Kern County Statistics Department. A review of the certificates of death for several other known maternal deaths found no comment on the certificate that they were pregnancy-related. Consequently, they had not been included in the maternal mortality statistics.

Certificates of death should include a box where the last pregnancy date could be noted. If a patient dies while pregnant, the date will signify it. If a patient dies two weeks after giving birth, that date will alert statisticians that the new mother's death may be related to the pregnancy. For example, a 21-year-old woman died ten days postpartum and autopsy confirmed mitral stenosis and calcification of the porcine valve which occurs when porcine valves are inserted in women younger than 16 years who subsequently become pregnant.[1] Without the pregnancy the complications probably would not have happened. It was a pregnancy-related death yet no mention of her recent pregnancy was included on the certificate of death.

We suggest that including a place for "date of last pregnancy" on certificates of death would result in more accurate maternal mortality statistics.

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1. Barnes AD, Van Geem TA, Johnson DM, et al: Postpartum complications with porcine heart valve—The age factor. The Female Patient 1986 Mar; 11:29-32

Chemical Denervation for Hemifacial Spasm

TO THE EDITOR: In the July issue Burchiel discusses the success of treatment of cranial neuropathies caused by microvascular compression via posterior fossa craniectomy.[1]

It may be worthwhile pointing out that for hemifacial spasm, chemical denervation induced by extremely small doses of botulinum toxin is an alternative therapy. This procedure has been introduced by Scott and co-workers[2] and has been used successfully in the treatment of blepharospasm as well as hemifacial spasm.[3] There have been no serious side effects and the injections are done on an outpatient basis.

This method of treatment has the obvious advantage of avoiding a craniectomy. The disadvantage is that the treatment produces a paresis that lasts only two to three months and repeated treatments are necessary. The repeated treatments appear, however, to be well tolerated by patients.

Since there is not insignificant morbidity associated with posterior fossa operations, this alternative should be offered to patients with hemifacial spasm.

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Treatment of Mushroom Amanitin Poisoning

TO THE EDITOR: We have three comments on the excellent paper by Pond and co-workers on mushroom amanitin poisoning in the August issue.[1]

Biliary recirculation of amanitin toxins was treated by duodenal tube and by activated charcoal. In a November 1983 poisoning—not reported in the series—Dr Larimore Cummins, a Santa Cruz, California, gastroenterologist, cannulated the common bile duct of a patient who survived *Amanita phalloides* poisoning. Where available, this procedure should be considered in severe poisonings as bile-laden amatoxin is totally diverted.

One mushroom cap from the collection eaten by patients 9 through 22 was in fact available at Brookside Hospital (San Pablo, California) and was identified as *Amanita phalloides* by one of us (P.V.), who also found strongly positive findings on a Meixner test.

Finally, there is now one paper available[2] on 205 consecutive European poisonings, where the use of intravenously given penicillin-G sodium resulted in a statistically significant decline in mortality. This study by Floersheim and coworkers is the largest series to date, and carefully analyzed by multiple regression. Previously, sufficient numbers of patients to statistically evaluate have been lacking in all published series. Thioctic acid appeared to be associated with an excess mortality, but one cannot rule out adverse selection. The intravenous administration of 40 million units a day of penicillin, therefore, is an option that may be considered.

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Manipulative Therapy for Low Back Pain

TO THE EDITOR: It would seem that the sheer magnitude of the suffering and cost of low back pain to our society would mandate that allopathic and osteopathic communities would finally unite on the issue of manipulative therapy.

To that end, let us share some observations that may apply and that we hope may encourage further dialogue.

Fifteen osteopathic medical schools are teaching subjective and objective methods for diagnosing spinal malfunctions leading to pain and disability. Additionally, their students are being taught the osteopathic principles involved in specific treatment. From there, it is hoped that they are trained in the skills to treat "hands on" for the dysfunction.

Manipulative therapy, being noninvasive, has a low morbidity risk. Outcomes, though occasionally dramatic, usually are consistent with "dosage" and patient cooperation.[1] As in any treatment modality, specificity of diagnosis contributes greatly to effectiveness. Recent manipulative research protocols[2] have standardized treatment, and outcomes are consistent and largely predictable. Postgraduate courses in osteopathic principles and practice are available at virtually all osteopathic medical schools for physicians interested in "hands on" experience.

Manipulative therapy adds another modality to the armamentarium of physicians using drugs, surgical treatment and other physical modalities—quite frequently a highly effective modality, indeed.

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Applying Information Technology to Clinical Medicine

TO THE EDITOR: The fascinating case of glucagonoma reported by Bolt and co-workers in the June 1986 issue[1] presents the tragic story of a man tormented by symptoms for more than a decade until an astute physician equated "sore tongue," "chronic indigestion" and "variable, red rash" with the possibility of an islet cell tumor. The patient underwent extensive evaluation at a university center documenting the presence of a glucagonoma. Ironically, the man subsequently died of complications of treatment.

The authors point out that the 12-year delay in diagnosis is typical of illness due to islet cell tumors. Surprisingly, they blame "the recent emphasis on cost effectiveness" as a "factor inhibiting early diagnosis."

The patient had been seen by numerous physicians, including appropriate subspecialists, for more than 12 years before anyone knew what was wrong with him. I seriously doubt that glucagon levels were not obtained for reasons of cost containment. More likely, the physicians did not think seriously about the possibility of glucagonoma. Or, if they did, they erroneously discounted the idea because they were unaware that more than 10% of patients with these tumors do not present "classic" features described in the medical literature.

The cost of this poor man's illness included 12 years of unmitigated morbidity, plus the cost of numerous useless investigations including multiple glucose tolerance tests, multiple skin biopsies, radiographic evaluation of the entire gastrointestinal tract and gallbladder, endoscopic evaluation of the stomach, small bowel and sigmoid colon, abdominal ultrasonograms and routine blood tests. Even after the diagnosis had been suspected and chemically confirmed by a glucagon level of 2,400 pg per ml, the man underwent additional tests including computer-assisted tomography of the head and abdomen with and without contrast; measurement of serum levels of amino acids, gastrin, insulin, vasoactive intestinal peptide, pancreatic polypeptide, cortisol, thyroxine, free thy-

roxine index, electrolytes, calcium and phosphorus; measurement of triiodothyronine uptake, and another glucose tolerance test. There is no comment on the cost effectiveness of these studies, nor who paid for them. There is no mention of anatomic or chemical assessments of the hepatobiliary system which subsequently was involved in the patient's death. Clearly, testing per se was not wanting in this case.

The delay in diagnosis in this patient resulted from two very common deficiencies in modern medicine: the failure of physicians to equate an illness with a recognized but rare condition and the failure of described "disease entities" to accurately reflect important and accessible details of observed illness. For 12 years, numerous physicians failed to equate the patient's case with a possibility of an islet cell tumor, whereas classic descriptions of islet cell tumors failed to include almost all the major descriptors of the patient's illness.

Despite all the costly investigative activity before and after the patient's diagnosis and the publication of an excellent case report, nothing has been done to address either of these problems.

The authors' admonition that "clinicians should be more alert to the forme fruste manifestations of these syndromes" does not solve the basic problem arising from the limited number of neurons in the human brain. While rare doctors exercise truly awesome memory capacities, the common lot of less gifted physicians currently has responsibility for many people's medical welfare. Eventually, as the number of important details in clinical medicine multiplies, even the best and the brightest minds will be overwhelmed. The solution is not better, brighter minds in medicine, nor more liberal use of exotic tests, nor further subspecialization; the only solution exists in the intelligent application of information technology to empower the otherwise-too-limited, unaided human mind.

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Treatments for Restless Legs Syndrome

To the Editor: It was with considerable interest that I read Drs Bernick and Stern's recent article on "Restless Legs Syndrome."[1] As a sufferer from this unlucky condition for many years, particularly in the late teenage years through my 20s and into my 30s, I frequently had considerable difficulty sitting down to read at night. On many occasions I read standing up and even occasionally doing toe stands to alleviate the "jitters." The problem is particularly bad when one wants to read. I seem to have inherited this condition from my mother, who called it the "jitters," who seemed also to have it at the same time of day, generally evening, with similar discomforts.

Nothing was successful in my treatment; I cannot even recall all the therapies tried over the years. Luckily I came to Stanford University in the late 1960s to finish my residency in plastic surgery. It did not take very long, living in California, to find out that a single glass of red wine at night seemed to totally alleviate my problems. Once a sufficient concentration of whatever-it-is is reached, one or two glasses a week suffices. When I passed this on to my mother, she was more than happy to try the treatment and was also totally relieved of the problem for the remaining ten years of her life. I do not know whether Salvatore Lucia, MD, late Professor of Medicine at the University of California, San Francisco, ever discussed this in any of his many books on the uses of wine in medicine, but it certainly should have been included. As the authors of this article are strongly recommending against jumping into those medications prescribed in the past, perhaps this is a treatment that others would like to try first.

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REFERENCE

1. Bernick C, Stern LZ: Restless legs syndrome. West J Med 1986 Aug; 145:263-265

* * *

To the Editor: My wife had a bad case of restless leg syndrome.[1] It disappeared when she quit taking calcium with magnesium supplements. She now takes calcium *only* and has no problems.

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1. Bernick C, Stern LZ: Restless legs syndrome. West J Med 1986 Aug; 145:263-265

* * *

To the Editor: The August article by Bernick and Stern on the restless legs syndrome discusses in detail the clinical features, etiology and treatment of this distressing entity.[1]

My medical specialty is dermatology and my interest in the restless legs syndrome was the result of two factors: one of my office employees had suffered from this condition for several years and my wife and I were both victims of nocturnal leg cramps. I was treating a young man for a skin problem with vitamin E in large doses, which relieved his dermatosis. As I reported in this journal in 1969, he was particularly grateful because this treatment also relieved him from severe cramps of various muscles that followed heavy exercise.[2]

In view of the striking results in the relief of exercise cramps with vitamin E therapy, I started my office nurse on the same treatment with prompt relief from her restless legs syndrome[3] and prescribed vitamin E for my wife and myself with prompt relief from our nocturnal leg cramps. The conditions remained under control with continued smaller maintenance doses of vitamin E, which I found were equally effective in controlling rectal cramps and intermittent claudication.

I am currently treating with vitamin E a 39-year-old man who has suffered from the restless legs syndrome for the past 28 years every day or night, occasionally three or four times in 24 hours. I prescribed vitamin E in the form of *d*-α-tocopheryl acetate, 400 IU to be taken three times a day before meals. At his most recent visit, nine months after his first visit, he stated that he had had only nine attacks of restless legs syndrome during the preceding two months, lasting only five to ten minutes.

I have treated a number of additional patients with restless legs syndrome with large doses of *d*-α-tocopheryl acetate or succinate with equally satisfactory results. The mechanism involved in the effectiveness of vitamin E in this condition is unknown but one of the primary functions of vitamin E is that of an antioxidant, protecting cell membranes of all tissues from lipid peroxidation, releasing free radicals that destroy the cells, liberating enzymes that, according to one theory, combine with certain tissue proteins, altering them so that the body produces autoimmune antibodies that cause various autoimmune diseases. This may be the mechanism involved in the response of the restless legs syndrome to vitamin E.[4]

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Topics in Primary Care Medicine

Therapeutic Drug Monitoring

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
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Series' Editors

The use of therapeutic drug monitoring is a relatively new phenomenon. Immunoassay and liquid chromatography techniques have made plasma drug level measurements widely available only since the late 1960s. The number of drug concentrations measured at the two major Boise, Idaho, hospitals increased more than fivefold from 1982 to 1985. Despite the fact that the use of these tests is rapidly accelerating, many physicians remain unschooled in their use.

Rationale for Therapeutic Drug Monitoring

Therapeutic drug monitoring is helpful in those situations in which (1) dosage cannot reliably predict serum concentrations, (2) the serum concentration has been well correlated with efficacy and (3) the therapeutic "window" of the drug is very small. Given our huge drug armamentarium, there are surprisingly few medications that meet these criteria. Most drugs are either fairly safe, not extensively studied or have other indices (such as the prothrombin time with warfarin) that provide a direct indication of therapeutic response.

Clinical Indications for Monitoring Drug Concentrations

Given that a drug meets the above three criteria, what are the specific clinical situations in which therapeutic drug monitoring is indicated? There are four major settings in which it may be helpful to determine drug concentrations. First, therapeutic drug monitoring is indicated when starting a drug regimen, changing the dose or in other situations when serum concentrations may be changing, such as conditions of fluctuating hepatic or renal function, and if a new, possibly interactive, drug is added. The prescribing of quinidine for someone on a digoxin regimen or of cimetidine for someone taking theophylline are two of many examples in this category. Second, drug levels may be used to investigate possible toxicity. Third, therapeutic drug monitoring may be used to assess patient compliance. Unless a patient's drug concentrations are monitored under controlled circumstances, however, it is difficult to determine absolutely whether low levels are due to noncompliance or to aberrant pharmacokinetics.

Finally, when a patient's symptoms are controlled, it is reasonable to check the serum concentration of a drug. This will provide a good indication of the therapeutic level for that person. If symptoms recur one can then better judge whether this recurrence is related to an altered drug concentration versus other factors. The routine periodic monitoring of levels in an asymptomatic patient is to be discouraged.

Timing of Therapeutic Drug Monitoring

When measurement of a drug concentration is indicated, a major source of error arises from the improper timing of collection. These errors of timing usually fall into one of three categories.

Failure to Attain Steady State

Whether a drug is given as a constant infusion or as interval doses, in most circumstances it will take at least four half-lives to reach 94% of steady-state levels. Digoxin, for example, which can have a half-life of up to 48 hours in patients with normal renal function, may take up to eight days to attain steady-state concentrations. Physicians must be careful to wait for steady-state conditions before collecting a specimen.

Failing to Allow for Distribution Phase

For drugs that are distributed to a large extent outside of the plasma space, serum concentrations will not always reflect the drug effect. Digoxin, for example, can take up to eight hours to equilibrate between the serum and target tissues, such as muscle. A patient who takes digoxin in the

(Bayer WH: Therapeutic drug monitoring. West J Med 1986 Oct; 145:524-527)

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morning and has a blood specimen drawn in clinic may be mislabeled as having toxic concentrations because the drug is still in its distribution phase.

Misinterpreting Peak and Trough Levels

It is safe to say that in judging overall efficacy, trough concentrations (predose) are easiest to interpret. This is particularly the case for those drugs with long half-lives (Table 1). In assessing the potential for toxicity, peak concentrations are usually more helpful. "Slow-release" medicines peak at about three to five hours, other oral medications at about two to three hours and drugs given intravenously at one hour. In many circumstances, it may be necessary to check peak *and* trough concentrations. This is true for aminoglycoside dosing and may also be the case for other drugs with short half-lives. If one is giving theophylline at intervals of one half-life, for example, a patient may have a trough level of 9 μg per ml and a peak level of 18 μg per ml. Measuring only a trough concentration in this circumstance may distort the actual therapeutic picture. Unfortunately, in most situations clinicians do not record whether a peak or a trough level is being measured. If the physician does not pay strict attention to the time of the last dose before a blood specimen is taken for drug monitoring, the result is often uninterpretable.

Finally, when adjusting drug dosages a clinician may usually assume a state of linear kinetics. Under this assumption clearance rates are independent of drug dosage and, thus, doubling a dose would result in an approximate doubling of steady-state concentrations. This assumption is not valid for phenytoin, salicylate or ethanol as clearance mechanisms can saturate in the pharmacologic dose range. Small dosage increments of these drugs can produce dramatic changes in serum concentration.

Interpreting Results

Even if the correct drug is monitored at the proper time, a clinician may encounter several pitfalls when interpreting the results. He or she must have a grasp of the importance of drug concentrations in each clinical situation. One must exercise great caution in the use of the aminoglycosides and theophylline, for example, because the therapeutic range is well defined. The therapeutic range has not been well defined for most of the anticonvulsants, however, and clinicians should monitor clinical efficacy without rigid adherence to somewhat arbitrary values. "Subtherapeutic" ranges may work well for some patients, while others may need "supratherapeutic" concentrations to attain efficacy. The importance of the therapeutic range for the most commonly monitored drugs will be discussed in the next section.

Physicians must also be cognizant of other variables that may affect clinical status. Electrolytes, for example, can influence the toxicity of digoxin. That is, a patient with hypokalemia can have severe digoxin toxicity with a "normal" digoxin concentration. Also, in a case of atrial fibrillation, the heart rate carries much more clinical significance than the digoxin value.

Commonly Monitored Drugs

In assessing the usefulness of monitoring drug concentrations for drugs that are monitored commonly, physicians should ask: Is dosage poorly correlated with serum concentration? Is serum concentration well correlated with efficacy? and Is there a low toxic to therapeutic ratio for this drug?

Aminoglycosides

Of the aminoglycosides, gentamicin sulfate has been studied most thoroughly. In patients with normal creatinine clearances, the serum half-life of gentamicin can vary from 24 to 450 minutes. Thus, serum concentrations cannot be predicted easily from dosage given.

Two retrospectives studies have analyzed the correlation between attaining therapeutic aminoglycoside concentrations and survival from documented Gram-negative bacteremia (Table 2).

The risks of ototoxicity and nephrotoxicity are both substantially increased when even moderate elevations of peak (more than 12 μg per ml for gentamicin or tobramycin) or trough (more than 2 μg per ml) concentrations persist. These toxicities are potentiated when there is increased noise, in cases of renal failure or with the concomitant use of drugs such as furosemide and ethacrynic acid. The aminoglycosides have a narrow therapeutic window and thus fulfill the three major criteria for meaningful drug monitoring. Clinicians should adhere closely to the therapeutic range.

TABLE 1.—*Drug Monitoring Indices*

Drugs	*Sampling Time(s)*	*Half-Life, hours*	*Therapeutic Range, μg/ml*
Antibiotics			
Gentamicin sulfate (tobramycin)	Predose, 1 h postdose	0.5 to 15	6 to 10 (<2 predose)
Amikacin	Predose, 1 h postdose	0.5 to 14	20 to 30 (<4 predose)
Anticonvulsants			
Phenytoin	Predose	9 to 100	10 to 30
Carbamazepine	Predose	5 to 65	8 to 12
Valproate sodium	Predose	6 to 17	50 to 100
Phenobarbital	Predose	60 to 120	10 to 40
Cardiac			
Digoxin	>8 h postdose	36 to 48	0.8 to 2.0*
Lidocaine	Anytime	1.5 to 2.2	1.5 to 5.0
Procainamide hydrochloride	Predose	3 to 5	6 to 14
Quinidine	Predose	6 to 7	1.5 to 6
Theophylline	Predose, 2 to 4 h postdose	4 to 10	10 to 20

*Nanograms per milliliter.

Anticonvulsants

Phenytoin is the most thoroughly studied drug in this class. The same dose can result in as much as a 50-fold difference in serum concentrations between patients. In addition, because clearance mechanisms can easily be saturated, small changes in dose can result in large changes in serum concentration. A clear relation exists between increased therapeutic levels and increased efficacy. The therapeutic window for phenytoin, however, is not as narrow as for other drugs. Because phenytoin concentrations of between 20 and 30 μg per ml rarely produce major toxicity, the need for close monitoring may not be as strong as for more toxic medications. Conversely, many patients may remain seizure free at "subtherapeutic" concentrations.

Fewer data are available concerning the efficacy of drug level monitoring with other anticonvulsants. In particular, valproic acid concentrations have not been shown to correlate strongly with efficacy. Some authors have hypothesized that this lack of correlation is related to the wide variability in the unbound, or "free," levels of valproate. A relation has been described, however, between increased concentrations and hepatic and renal toxicity. Monitoring may be justified to guard against complications.

Carbamazepine is rapidly absorbed and thus may show side effects despite documentation of "therapeutic" levels. For this reason, some authors have recommended very frequent dosing while others have had success with a single dose given at bedtime.

In general, there is a great deal of interaction between the various anticonvulsants, and concentrations can change dramatically when a new drug is added. In addition, most of the medications stimulate an "autoinduction" of hepatic enzymes so that levels may gradually decrease over several months.

Theophylline

The unpredictability of theophylline concentrations is widely recognized, particularly in smokers and in those with concomitant hepatic or cardiac disease. Attaining high therapeutic concentrations is beneficial in cases of status asthmaticus, but probably not helpful during long-term treatment of asthma. Serum theophylline levels as low as 25 μg per ml can precipitate seizures and most patients with theophylline levels above 20 μg per ml will have symptoms of toxicity. Theophylline generally fits the basic criteria for drug monitoring.

TABLE 2.—*Early Peak Aminoglycoside and Survival From Gram-Negative Bacteremia*

Two Studies, Early Peak Level	*Outcome*	
	Died, Number (Percent)	*Survived, Number (Percent)*
Noone et al, 1974		
Therapeutic*	1 (11.1)	10 (88.1)
Subtherapeutic	4 (100)	0 (0)
Moore et al, 1984		
Therapeutic†	1 (2.4)	40 (97.6)
Subtherapeutic	9 (20.9)	34 (79.1)

*At least one peak gentamicin sulfate level, measured within 72 hours of therapy, greater than 5 μg per ml.

†First peak aminoglycoside level, obtained within 48 hours of therapy, greater than 5 μg per ml for gentamicin or tobramicin, or greater than 20 μg per ml for amikacin.

Digoxin

There is poor correlation between predicted and actual digoxin concentrations. In addition, therapeutic efficacy is enhanced when digoxin levels are higher than 1 ng per ml. About 85% of patients with digoxin concentrations greater than 2.0 ng per ml will have symptoms or electrocardiographic signs of toxicity. A 50% decrease in digoxin toxicity was noted upon instituting digoxin monitoring at Massachusetts General Hospital. When interpreted in conjunction with a patient's overall clinical state, digoxin concentrations appear to be helpful.

Ventricular Antiarrhythmics

There is poor correlation between antiarrhythmic drug levels and dosage, with as much as a tenfold variation in serum concentrations among patients taking the same dose of procainamide. The relationship between serum concentrations and clinical efficacy, however, remains unclear. Indeed, the overall clinical efficacy of the antiarrhythmics is somewhat unclear. Although these drugs have been shown to resolve dysrhythmias, controlled studies have not been done that document an effect on mortality.

Even when correlating drug levels only to a decrease in ventricular ectopy, a great deal of controversy persists. Major problems include poor standardization of sampling times, inconsistent measures of efficacy and an unclear effect of metabolites on results. Concentrations associated with toxicity, on the other hand, are more clear. Drug monitoring then, is probably justified to rule out possible toxicity.

The original therapeutic drug monitoring studies of quinidine looked at efficacy for atrial fibrillation and their findings may not apply to that of the treatment of ventricular arrhythmias. In addition, the earlier drug levels were probably also measuring inactive quinidine metabolites, so that the range of efficacy is probably lower (1.5 to 6 μg per ml) with recent, more specific, assay techniques.

Procainamide hydrochloride is one of the best studied antiarrhythmics. The original studies indicated a therapeutic range of 4 to 8 μg per ml, but subsequent studies have shown the need for higher levels, between 6 and 14 μg per ml, especially in patients with underlying heart disease. The interpretation of levels of a major metabolite, *N*-acetylprocainamide, which has distinct antiarrhythmic properties, is controversial. Recommendations have ranged from summing the procainamide and *N*-acetylprocainamide levels to ignoring the *N*-acetylprocainamide level. The latter recommendation seems most reasonable as the major clinical studies did not look at *N*-acetylprocainamide concentrations. Because it is excreted by the kidney, however, levels should be monitored in patients with renal failure to avoid toxicity.

Lidocaine toxicity at concentrations greater than 6 μg per ml has been well documented, and therapeutic drug monitoring may be indicated in cases of congestive heart failure or old age. Drug monitoring guidelines for disopyramide and bretylium tosylate have not been well delineated. Because of erratic protein binding, total drug concentrations may be a poor indicator of drug effect. Toxic levels also remain unclear.

Future Considerations

The major anticipated improvements in therapeutic drug monitoring will come from the development of computer-

guided dosing and the use of "free" drug levels. Because of the inability of clinical intuition or nomograms to predict desired drug dosages, many authors have turned to computer-guided decision-making. In these schemes, a patient's early response to an initial drug dose can be used to create an individual pharmacokinetic profile. Such a method may improve substantially on clinical estimates of drug dosing. The use of "free" drug concentrations would seem to reflect efficacy more closely because the drug that is directly available to target sites is the unbound portion. Free level measurements, however, are more difficult, expensive and prone to laboratory error. As techniques improve it seems likely that free drug concentrations will be used more frequently. Current indications seem to arise mostly in cases of altered protein-binding states (such as hypoalbuminemia, renal or hepatic disease, pregnancy and the use of multiple drugs) and the concomitant use of drugs that compete for the same binding sites.

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Seminars in Health Care Delivery

The Medicare Prospective Payment System

Technical Adjustments and the Role of ProPAC

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This feature will appear regularly in The Western Journal of Medicine. *It is intended to cover recent developments in a broad range of issues that will have an impact—either directly or indirectly—on clinical practice. Occasionally the seminars may include informed speculation about likely future developments.*

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While Medicare's Prospective Payment System (PPS) has been controversial since its inception in 1983, few would question that it has the potential for generating the most far-reaching changes in our health care system since passage of the original Medicare law itself. The originators of the plan hoped to develop a system that would control if not reduce the rate of Medicare spending while maintaining the quality of hospital care and access to that care by Medicare beneficiaries. To do this, the PPS system pays hospitals a predetermined fixed amount based on the diagnosis of the illness that was primarily responsible for the patient's hospital admission, adjusted for certain characteristics of the patient—such as age and sex, and in some instances whether there are complicating factors.

Incentives of the New Payment System

By separating the payment amount from the resources used to treat a particular patient and using as the unit of measurement the complete hospital stay as opposed to the previous Medicare unit, each day of care, the new system substantially changes the financial incentives faced by hospitals. Of particular interest are the incentives to reduce the length of time patients stay in the hospital and limit the amount of resources and procedures that are used to treat patients during their hospital stay. Both factors have been singled out in the past as "culprits" in the tremendous increases in hospital costs during the 16 years following passage of Medicare and Medicaid.[1]

Many students of the US health care system, however, have become very concerned about the reversal of the financial incentives embodied in this new law. While few would recommend a return to the previous system which included very few incentives to provide medical care efficiently, they are apprehensive about a system that flips these incentives "on their ear" and puts tremendous pressure on hospitals to provide as little care as possible. Unlike a comprehensive capitated system, which has some of the same incentives, PPS does not include the same marketplace safeguards that are contained in capitated plans. Plans that provide too few services are threatened with the possibility of losing many of their members. There is also the possibility that if an illness is not appropriately treated at the outset, it could cost the plan many more dollars later in the medical cycle. Of course, PPS is not without its own safeguards which include the ethical commitments of physicians who still have the same professional and financial incentives to demand the best available treatment for their patients. But for the first time since 1965, a real tug of war could exist in certain situations between the demands of patients or their physician and the financial requirements of the hospital.

One of the strongest arguments made by the Reagan Administration in recommending the PPS approach to the Congress was that it would promote competition in the health care system and reduce the regulatory requirements of the federal government. While I believe that PPS does have the potential to foster a much greater degree of competitive forces than the previous system, many of these are not automatic or self-correcting as they would be in an Adam Smith-type free market and they require frequent technical adjustment by government. To a large extent, I believe, the success of PPS to encourage the efficient delivery of hospital care without causing serious declines in the quality of care will depend on how well these so-called technical adjustments are made.

Prospective Payment Assessment Commission

Congress, realizing the negative potentials of PPS and recognizing that it and the executive branch could use help in making these technical adjustments, created the Prospective

(Altman SH: The Medicare prospective payment system—Technical adjustments and the role of ProPAC. West J Med 1986 Oct; 145:528-534)

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An earlier version of this paper was delivered at the University of California, Berkeley, School of Public Health on October 3, 1985.
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ABBREVIATIONS USED IN TEXT

DAF = Discretionary Adjustment Factor
DHHS = Department of Health and Human Services
DRG = diagnosis-related group
HCFA = Health Care Financing Administration
MRI = magnetic resonance imaging
PPS = Prospective Payment System
ProPAC = Prospective Payment Assessment Commission

Payment Assessment Commission. ProPAC, as it is called, was mandated by the same law that created the PPS/DRG (diagnosis-related groups) system and was put in place to evaluate the effects of PPS and minimize any negative consequences. It was to include members knowledgeable about the Medicare program and the US health care system. The initial group of 15 members were appointed by the director of the Office of Technology Assessment in November 1983 and I was asked to be its chairman. The commission's role is to advise the executive and legislative branches of the government on the operation of the PPS and to provide analysis necessary to maintain and update the system. The Commission has two primary responsibilities:

- Recommend annually to the secretary of the Department of Health and Human Services (DHHS) the appropriate percentage change in the Medicare payments for inpatient hospital care; this percentage change is called the "Update Factor";
- Consult with and recommend to the secretary of the Department of Health and Human Services necessary changes in the diagnosis-related groups (DRGs), including advice on establishing new DRGs, modifying existing DRGs and changing the relative weights of the DRGs.

The first requirement, that of recommending an appropriate *update factor* to the previous year's rate, was to be accomplished by April 1 of each year. This would permit the secretary of DHHS to incorporate the commission's recommendations into the proposed and final regulations that are due by October 1 of each year. The commission has met its deadline for each of its first two reports.

Underlying the substance of the April report is the issue of whether the existing DRG system is an adequate base for compensating hospitals overall and whether there are structural aspects of the DRG system that discriminate against or in favor of specific types of patients or hospitals. If either or both indicate problems it is the responsibility of the commission to recommend appropriate technical adjustments. The commission has also indicated its willingness to consider at times more fundamental reforms if the problems appear serious enough or if previous technical adjustments have been unsuccessful in solving the problem.

Annual Adjustment in DRG Rates

The mechanism used by PPS to provide hospitals with yearly changes in the payment rate per DRG patient is the Annual Update Factor, which can be defined by the following equation:

$$\text{Annual Update} = \text{Hospital Inflation (Market Basket)} + \text{Discretionary Adjustment Factor (DAF)}$$

It is through changes in this annual update factor that Congress and the administration will decide how much this country is willing to support the continuous growth in the American hospital system, which had been growing two to three times faster than the national economy. While the hospital inflation factor is relatively straightforward and is based on technical estimates of expected inflation for the various resources used by hospitals, the DAF component is complicated and very difficult to measure. In principle, DAF is to include a *negative* adjustment for expected or real improvements in hospital productivity and a *positive* adjustment to permit hospitals to incorporate new technological and scientific advances and to assure that the quality of care and access to hospitals is maintained at an acceptable level.

Estimating Inflation

One issue the commission focused on in deciding the appropriate inflation rate is whether a hospital's market basket should vary by region of the country. The market basket used by the Health Care Financing Administration (HCFA) included the same 18 categories of expenses for all areas of the country. What's more, the same relative weight (or importance factor) was used throughout the United States, except for area wage differences. As shown in Table 1, wages as a proportion of total expenses vary by region as well as whether a hospital is within a major urban area. Other evidence showed that wage changes also vary by region.[2(pp 31-35)] Therefore, it seemed important to the commission that separate regional wage factors be maintained.

But what about the other components of expenses? My own view was that some variation in the non-labor expense categories might be appropriate to assure equity across hospitals. After all, fuel oil is likely to be more important in New England than in the South. A review of the evidence, however, did not support the need for such an adjustment. A study published in 1981 concluded that between 1972 and 1979 no significant differences existed between increases in the national input price index and increases in the regional input price index.[2(p 31)] A second major conclusion was that to the extent that there were variations in the increase in the market baskets across regions, the primary cause was differences in price changes. Differences in the market basket weights had very little effect. It was this study that provided the basis for HCFA's decision not to include regional variations for non-labor expenses. The commission was concerned, however, that if overall inflation were to increase sharply above the limited inflation reflected in the 1972-1979 period, these conclusions might not hold. For example, when the price of silver went through the roof in the early 1980s, those tertiary care hospitals using x-ray and other diagnostic testing faced much larger than average price changes. ProPAC, therefore, in its first report, recommended an ongoing study to determine if multiple regional market baskets would be necessary in the future.[3(pp 30-31)]

No easy consensus emerged with respect to the discretionary adjustments. The PPS legislation of 1983 called for a +1.0 percentage point increase to provide hospitals with continued capital for technological and quality improvements. Under a later Deficit Reduction Act this add-on was revised downward by the Congress to +0.25% percentage point for 1985 and a ceiling of 0.25% was established for 1986. The Congress left open what those rates should be for future years.

Productivity Factor

A review of the literature provided little help in sorting out the various influences affecting hospital productivity and what an appropriate technology/quality adjustment should be. With respect to productivity, it was clear to the commission that past experiences were of limited help because the incentives were primarily to enhance perceived quality of care and access and very limited rewards existed for increasing efficiency of operations or reducing costs. It therefore seemed more reasonable to use the productivity component to "reflect a policy target which encourages the attainment of the highest level of productivity that is compatible with high quality patient care and long-term cost effectiveness of the health care system."[2(p49)]

Some have questioned whether it is appropriate to penalize hospitals by lowering the price they receive because they have taken actions to increase productivity. The argument has been made that if all the productivity advances lead to ultimate price reductions, then there is no real incentive for hospitals to try to become more efficient. I think that argument is fallacious on three grounds. First, if no adjustment in price resulted from these productivity improvements, all we would have done with the PPS system is generate a substantial growth in hospital profits or retained earnings. Some sharing of these productivity advances must accrue to the buyers of care, the government and the patient. Second, in a competitive marketplace improved productivity is the key mechanism that generates price reductions—not because each producer wants it to happen, but because each wants to sell more of their expanded product and now can do so at a lower price. Finally, even with such reductions in price, a hospital would still benefit financially from improving the efficiency of its operations. Reductions in price take place only gradually over time and then are based on the average performance of all the hospitals. A hospital that is in front of the pack with such improvements and exceeds the average performance of the group will reap the rewards for a longer time period and will see a permanent advantage even after the average price falls.

While the DRG unit of measurement allows the basic hospital product to be relatively standardized, there is still the question of whether the product really begins and ends when a patient enters and leaves the hospital. The PPS system clearly provides a strong incentive to admit patients to the inpatient setting but to shift services out of that setting, both before and after a hospital stay. An important and often overlooked aspect of the system is that the initial dollar amounts for each DRG were based on the amount and duration of care provided on average to patients with the diagnoses grouped in that category before PPS started. Shifting of services to other settings may be a very appropriate and desirable outcome, but if no adjustment is made in the payment amount either directly through a recalculation of the costs in all of the DRG categories or through some adjustment in the annual update factor, then all the savings of such changes will accrue to the hospitals. Therefore, it seemed to us necessary to examine the changing patterns of care including the changing site where the services are provided. Reductions in the average length of a stay in the hospital can reflect both a real increase in hospital productivity as well as a change in the hospital product.

Quantitative evidence regarding practice pattern changes is not easy to obtain. During the initial year of investigation the commission was limited to changes in average length of stay. At the time the commission was reviewing these data they indicated that for the 65-year-old and older population length of stay had declined by 7.8% in the first nine months of 1984 as compared with the same period the year before. While such a decline continued a downward trend that has been going on since 1970 (see Table 2), the magnitude of the change following the introduction of PPS suggests a clear relationship. Translating this productivity improvement into expected cost reductions required a series of assumptions about the marginal costs associated with reduced lengths of stay. Using the 60% factor established in PPS to pay for the added cost of treating outlier patients, the 7.8% decline in length of stay resulted in an estimated 4.7% reduction in expenses. Using a conservative estimate that 1.0% of the reduction in expenses was the result of actual changes in hospital services, the commission concluded that productivity advances permitted hospitals to lower their costs by 3.7% without reducing the quality of patient care to Medicare bene-

TABLE 1.—*Relative Cost Weight* From Wages by Census Division and Hospital Classification (1977 Base Year)†*

Hospital Classification	US	Outlying Areas	New England	Middle Atlantic	South Atlantic	East North Central	East South Central	West North Central	West South Central	Mountain	Pacific
All hospitals	51.74	50.91	54.31	55.25	49.84	53.35	48.52	51.76	48.21	50.30	48.46
Teaching hospitals		52.35	55.07	56.22	52.03	54.84	50.40	52.51	51.82	52.89	51.80
Non-teaching hospitals		47.59	53.36	52.99	48.06	51.67	47.58	51.25	46.78	48.88	46.20
Hospitals in SMSA	52.06	N/A	54.58	55.36	50.05	53.77	48.63	51.89	48.28	50.50	48.57
Bedsize (less than 100)		N/A	50.35	50.39	47.71	49.41	46.27	52.19	44.97	43.97	42.52
Bedsize (100-404)		N/A	55.03	53.57	48.00	52.48	47.34	50.81	46.16	50.97	47.71
Bedsize (405-684)		N/A	55.03	55.66	52.20	53.86	49.39	53.03	51.91	51.06	51.35
Bedsize (greater than 685)		N/A	54.02	58.39	51.81	57.35	52.51	51.62	51.57	45.58	54.49
Hospitals located in non-SMSA	50.19	50.91	52.43	54.04	49.17	50.87	48.29	51.48	47.96	49.74	47.45
Bedsize (less than 100)		44.18	51.79	50.43	47.59	50.01	47.70	51.59	48.10	49.32	46.86
Bedsize (100-169)		47.91	52.45	53.19	47.66	50.35	48.25	51.01	47.63	49.52	48.12
Bedsize (greater than 169)		52.72	52.77	55.21	50.79	51.68	49.17	51.76	48.08	51.28	47.82

SMSA=Standard Metropolitan Statistical Area

*Relative proportion of total resources spent by a hospital.

†American Hospital Association, Annual Survey, 1977. Compiled by: Office of Research, Demonstrations, and Statistics, HCFA. Source: *Technical Appendixes to the Report, April 1, 1985,* Prospective Payment Assessment Commission, p 33.[2]

ficiaries. In an attempt to share these savings with the hospital industry, the commission recommeded that the next annual update rate should be reduced by 1.5% for productivity and further reduced by 1.0% for the product shift. HCFA in its final set of regulations for the 1986 update rate used similar logic and arrived at similar productivity adjustment numbers.[4(pp 44-59)] But they arrived at total update rate of 0% because they determined that hospitals had inappropriately inflated the case level of the patients they treated and thereby received an excess in total payments from the government. Congress, after much political "horsetrading" with the administration, provided hospitals with a 0.5% increase for 1986. In so doing Congress adopted many of the recommendations in ProPAC's first April report.

It was clear to the commission that future adjustments would require a better understanding of how these forces really operate or else hospitals would either reap inappropriate windfalls from PPS or be penalized unnecessarily. In its second April report the commission continued to use the same basic approach. Although length of stay reductions slowed to 2.9% compared with 7.8% the previous year, further productivity gains through less use of ancillary tests were observed. In total, the commission concluded that hospitals could reduce their costs by 1.5% through productivity gains.

An Allowance for Technological Change

The last aspect of the discretionary adjustment factor is the appropriate positive adjustment for providing hospitals with an allowance for new procedures, techniques or technologies to enhance the quality or access to the care they provide. This issue also ties in with the second major charge of the commission, that of recommending adjustments to the basic DRG structure of the system. Under the previous cost-based system, adjustments were instantaneous and complete and required no special mechanism; if some new procedure was considered appropriate, it was considered a covered service and its costs were immediately incorporated into the cost report and ultimately would be paid. Under PPS no such automatic adjustment exists. This is both a strength of the new system and a component that gives critics much to complain about. Left alone PPS will not pay a hospital any more money for either providing more traditional services to a patient or adding a new service which may be quality enhancing but which is cost generating. The question is, "How do you maintain this tight incentive to force hospitals and physicians to ask the question whether the extra test or procedure or day of care is really that necessary and yet assure that if the answer is truly yes, there will be funds to pay for it?"

The annual update adjustment for technology and quality is supposed to provide some financial cushion to allow the hundreds of small improvements in hospital care to continue, and to leave to a structural change in specific DRGs larger and more targeted changes. As shown in Table 3, after adjusting for hospital inflation and changes in admissions, hospital spending for inpatient Medicare services grew by 2.8% a year between 1972 and 1983. A major portion of this "intensity factor" was funds used by hospitals to buy quality-enhancing technologies. It also included spending for some items that had very marginal benefits to patient care. Clearly if hospital spending is to be reduced, some of this yearly "real" growth in hospital spending needs to be reduced. How much a reduction is appropriate is both a technical and a political question. That is, what will we lose by reducing such spending and are we as a country willing to pay the added cost of continuing to improve the level of medical care? The commission recommended in the first year update an amount equal to 50% of the average intensity factor for the past 12 years, or between 1.5% and 2.0%. In the second year annual update, this portion of the technology adjustment was reduced to 0.7% recognizing that the commission was recommending several adjustments to the DRG structure for technology or new medical procedures such as magnetic resonance imaging and more complicated cardiac pacemakers that would add to the total hospital payment amount.

In summary, the commission recommended that the update factor be equal to the estimated increase in the medical market basket plus a −1.0% for the Discretionary Adjustment Factor in 1986 and −0.5% in 1987. The commission also recommended that a further adjustment be included to the extent that hospitals had upgraded the coding weight for illness after PPS began. The commission felt that such coding adjustments not related to the treating of more sick patients will generate inappropriately higher payments to hospitals and should be taken back by the government before they are built into the hospital payment base. A major difference with HCFA developed over this issue for the 1986 adjustment as the executive branch sought to reduce the expenditure factor to compensate for such coding "creep" since the inception of PPS.[4(pp 18-25)] The commission felt the adjustment should be limited to such changes for only the previous year.

A comparison of the update adjustments recommended by ProPAC for 1986 and the approved HCFA adjustments are shown in Table 4. Also shown in Table 5 are the estimated ProPAC adjustments for 1987. If 1987 follows the same pattern as 1986, the administration will use only a limited

TABLE 2.—*Trends in Inpatient Hospital Length of Stay*

Calendar Year	Percent Change in Length of Stay: ALOS,* All Patients (Percent)	Percent Change	ALOS,* 65+ Patients (Percent)	Percent Change
1970	7.82	−3.08	12.62	−3.00
1971	7.66	−1.96	12.62	−3.10
1972	7.56	−1.38	11.74	−3.95
1973	7.44	−1.54	11.40	−2.92
1974	7.38	−0.81	11.31	−0.79
1975	7.38	0.04	11.23	−0.69
1976	7.37	−0.12	11.05	−1.62
1977	7.25	−1.74	10.71	−3.02
1978	7.22	−0.31	10.59	−1.20
1979	7.15	−1.05	10.39	−1.90
1980	7.18	0.47	10.38	−0.09
1981	7.21	0.37	10.36	−0.12
1982	7.16	−0.61	10.13	−2.27
aver. (1970-82)	7.37	−0.90	11.09	−1.80
1983	7.02	−2.04	9.68	−4.47
1984	6.66	−5.00	8.94	−7.60
1985 (8 mos.)	6.54	−2.10	8.74	−2.90
aver. (1983-85)	6.74	−3.10	9.12	−5.00

Source: *Technical Appendixes to the Report, April 1, 1985,* Prospective Payment Assessment Commission, p 14.[2]

*Average length of stay, in days.

number of the ProPAC recommendations as far as the update factor is concerned. Congress, on the other hand, is more likely to take the ProPAC recommendations seriously even though it might not accept the bottom-line recommendation. The commission, of late, has been required to defend its update recommendation as politically too high. At the same time some in the medical community feel ProPAC has been too tough in recommending increases less than the overall inflation rate. In commenting on the issue the commission stated in its 1987 report,

In the current environment of fiscal stringency an estimated 2.8 percent increase in PPS payment amounts for fiscal year 1987 may seem unduly high. Hospitals received no increase for the first half of fiscal year 1986, and may receive a net reduction for the second half of the year if the Gramm-Rudman-Hollings deficit reduction act is upheld. The President's proposed budget for fiscal year 1987 estimates a 2.0 percent increase in PPS payment rates. The Commission recommended increase is very stringent compared to historical trends in Medicare payments to hospitals, however. Between 1972 and 1983, these payments averaged about 3 percentage points *above* inflation, whereas the Commission estimates its recommendation for fiscal year 1987 to be 1.5 percentage points below inflation.[5(p 9)]

Changing the DRG Structure

Regardless of the decision on the update factor, providing hospitals with an overall cash allowance for new technologies does not guarantee that desirable new procedures or devices will be bought or used. These funds are ultimately usable for any purpose. Therefore, pressure continues to be placed on making adjustments in specific DRGs or adding new DRGs for a new procedure or device. In most cases a structural change decision is a two part decision. Is a change medically required; that is, does the new procedure add appreciably to the quality of medical care? If the answer is yes, the next question is how should the change be made? If a particular procedure is clearly focused on a specific type of diagnosis, a new DRG can be constructed, as HCFA proposed in 1986, for operations involving a bilateral hip replacement as opposed to a single hip operation. Alternatively, the new procedure can be moved to an existing DRG that closely reflects the new cost of treatment. The system also can be allowed to correct itself through periodic "recalibrations" of the actual costs incurred in treating all DRGs, or by "reweighting" a specific DRG to better reflect the new resource cost that includes the new procedure. An example of the latter is the growing use of intraocular lens implants for the treatment of cataract extractions. During the short period between 1981 and 1983 the number of extractions using the more expensive lens implants increased from 58% to 85%. The commission decided not to make any specific adjustments in DRG 39—Lens Procedures—but rather to allow the change to take place through a recalibration of the resource weights for all DRGs. This recommendation was followed by HCFA and the weight assigned to DRG 39 went up by more than 15%.

Two types of technology changes are not so easy to adjust for in PPS and could have long-term consequences in the years ahead. I would like to conclude this article with a discussion of what we should do with cases where there is more than one procedure or device that can be used for the same diagnosis, but where the resource costs are very different; and, how we should incorporate into the system new high-cost technologies or procedures that treat many different illnesses but are used only in a select number of hospitals.

Alternative Treatments for Same Diagnosis

Among the 468 active DRG categories are four used for patients with a heart condition that requires a pacemaker implant. Differences in the payment rate of the four DRGs relate to whether the implant is part of more extensive and complicated care, whether it is just focused on the implant surgical procedure or whether it is payment for an adjustment or replacement of the pacemaker. To complicate the story, there are also four different types of pacemakers which vary considerably in expense. The current PPS does not recognize any difference in device cost expense. In 1981 there were 15% of implant patients who had the least expensive "single chamber nonprogrammable" pacemaker and 6% who had the most

TABLE 3.—*Historical Annual Percentage Changes in Medicare Inpatient Hospital Costs, 1972-1983, and Projections for 1984 and 1985, by Components*

Calendar Year	Medicare Inpatient Hospital Costs (Percent)	Market Basket			Medicare Admissions			Inpatient Costs Per Admission (Percent)	Intensity (Percent)
		Hourly Earnings Hospitals (Percent)	Nonlabor Inputs (Percent)	Total (Percent)	Medicare Enrollees (Percent)	Admissions Per Enrollee (Percent)	Total (Percent)		
1972	10.9	6.8	4.5	5.9	1.4	1.2	2.6	8.1	2.1
1973	16.4	5.5	8.0	6.5	6.5	7.1	14.1	2.0	−4.2
1974	23.6	7.7	14.2	10.4	6.2	0.3	6.5	16.1	5.1
1975	22.5	9.9	12.2	10.9	3.4	0.1	3.5	18.4	6.7
1976	19.0	8.2	8.3	8.2	2.9	1.5	4.4	14.0	5.3
1977	17.3	7.1	7.9	7.4	3.0	4.5	7.6	9.0	1.5
1978	14.8	8.4	7.9	8.2	2.7	−1.8	0.9	13.8	5.2
1979	16.4	8.4	11.1	9.6	2.7	2.9	5.7	10.1	0.5
1980	20.3	10.6	12.8	11.6	2.1	2.4	4.6	15.0	3.1
1981	21.6	12.3	11.2	11.8	1.9	1.8	3.7	17.3	4.9
1982	16.1	11.0	7.3	9.4	2.1	1.9	4.0	11.6	2.0
1983	13.0	7.2	4.8	6.2	1.5	3.1	4.6	8.0	1.7
Average	17.6	8.5	7.7	8.8	3.0	2.1	5.2	11.7	2.8
Projections:									
1984	11.8	6.4	4.4	5.9	1.8	2.0	3.8	7.7	1.7
1985	12.5	7.7	4.6	7.1	2.1	2.0	4.1	8.1	0.9

From the 1984 Annual Report of the Board of Trustees of the Federal Hospital Insurance Trust Fund, April 1984, Table A1, p 53.
Source: *Technical Appendixes to the Report, April 1, 1985,* Prospective Payment Assessment Commission, p 51.[2]

expensive "dual-chamber programmable" model. By 1984 these utilization figures were reversed with only 3% having the least expensive model and 26% the most expensive unit. In 1984 the cost of the most expensive model was almost twice as high as the lowest cost unit ($5,171 versus $2,741). In addition to differences in device costs, there are also related differences in the surgical and physician cost of implantation. Question: How should the changes from 1981 to 1984 be reflected and, more important, should the DRG price reflect differences in the device costs?

The first part of the question is similar to the intraocular lens issue and the commission ruled the same way (for example, let recalibration adjust for the changes), but the second part is complicated and has no easy answer. If the DRG prices vary based on the device or resources used in the treatment, then the system has backed into the same set of incentives that existed under cost based reimbursement. If no adjustments are made and hospitals are paid based on the average of all the potential devices, then for those patients who are treated with the least expensive model the hospital is paid too much and for those patients implanted with the most expensive model, the hospital incurs losses. In part, I believe we want a payment system that forces hospitals and physicians to question whether the most expensive device or procedure is really that necessary. But we do not want the system to so penalize hospitals for a particular type of care that they are compelled to deny such services to some patients who need them and who would, on their own, be willing to pay the added expense. Thus far, neither HCFA nor the commission has come up with an acceptable solution. My own view is the PPS needs a payment mechanism for situations such as this where the hospital has some financial incentive to use the least costly device, but where the losses of using the most costly device are limited and could be absorbed by the hospital, if they wished, from the technology allowance in their update factor.

One possible mechanism to accomplish this is to divide the hospital payment into two parts. The first would reflect the average resource cost for treating all patients with a similar diagnosis; the second would be tied to the specific resources used to treat that particular patient.* In the case of a pacemaker patient such a revised DRG payment would limit the loss to the hospital that implanted the most costly device to the equivalent of a 12.5% coinsurance rate assuming that there were just the high and low cost models and each was used about the same amount. Such a rate while high enough for a hospital to question a physician who always used the most expensive device would still be low enough to permit any patient who needed the more expensive model to receive it. It should be remembered that under current law a patient can *not* agree to pay the hospital a *supplemental* amount to insure that he or she gets the most expensive model. If the PPS payment is not adjused to reflect a higher rate for certain procedures or devices, I think pressure will build to allow such supplemental payments. Advocates of one-class medicine will fight against such a move since patients with limited income could not afford to supplement the Medicare payment.

During debate on its 1987 recommendations, ProPAC briefly considered such a proposal and rejected it in favor of requesting that HCFA split the pacemaker DRGs to reflect whether the patient was given a single chamber or a dual chamber pacemaker.[5(pp 99-102)] If HCFA rejects this recommendation and Congress does not overrule them the blended rate adjustment may yet be used for certain types of patients.

TABLE 4.—*Estimated Increase in PPS Payment Amounts for Fiscal Year 1986: Comparison of HCFA to ProPAC Recommendations*

Increase in Payments	*HCFA (Percent)*	*ProPAC (Percent)*
FY 86 Market Basket increase	4.85	4.85
Previous Market Basket forecast errors	−1.30	−0.57
Policy Target Adjustment Factor (DAF)	−1.50	−1.00
Components:		
Productivity	−1.00	−1.5 to −2.0
Cost-effective technologies	1.50	1.5 to 2.0
Product change		−1.0
Cost-ineffective practice patterns	−2.00	
Subtotal (Market Basket+DAF)	2.05	3.28
Observed change in case mix	−4.90	−2.00
Real case-mix change during FY 85	0.00	0.80
Total	−2.85	2.08
Proposed increase	0.00	2.08

Source: *1986 Adjustments to the Medicare Prospective Payment System, Report to the Congress, November 1985,* Prospective Payment Assessment Commission, p 19.[4]

TABLE 5.—*Recommended Projected Payment Assessment Commission Increases in PPS Payment Amounts for Fiscal Year 1987*

Recommended Increase		*1987 (Percent)*
Estimated Market Basket increase		4.6
Correction for Market Basket forecast errors in previous fiscal year		−0.3
Discretionary adjustment factor		−0.5
Scientific and technological advancement	0.7	
Productivity	−1.5	
Site substitution	−0.6	
Real case-mix change in fiscal year 1986	0.9	
DRG case-mix index	0.2	n.a.
Within-DRG patient complexity	0.7	n.a.
Subtotal (update in standardized amounts)		3.8
Observed change in case-mix index (adjustment made to DRG weights after recalibration)		−1.0
Total change in DRG prices		2.8

Source: *Report and Recommendations to the Secretary, US Department of Health and Human Services, April 1, 1986,* Prospective Payment Assessment Commission, p 19.

High Device Costs in Multiple DRGs

An example of the second problem area is the issue of how to pay for new diagnostic technologies such as magnetic resonance imaging (MRI). MRI is a very expensive technology costing up to $2 million per machine plus operating expenses. Even at maximum efficiency, the operating expenses alone equal about $130 per scan. It is likely that an MRI scan could be called for in more than 100 different DRGs, and therefore no specific DRG adjustment is possible. HCFA is proposing that no MRI adjustment be made, and that payments increase gradually through annual recalibration in those DRGs that use MRI scans. Such payments, however, will be available to all hospitals whether or not they have MRI and for all patients in those DRGs whether or not a scan was done. As such, for

*Suggested in an unpublished manuscript, "Restructuring the DRG System," by Prof Thomas McGuire, Department of Economics, Boston University, Boston, Massachusetts.

those institutions that do purchase a machine, the extra payments they receive will be far less than the cost of operating the equipment. Also, for those patients who do receive a scan, the payment level will only pay a small proportion of the added costs of the procedure.

What kind of signals will such a payment approach send to MRI manufacturers and, more important, to future manufacturers of expensive medical equipment? As an alternative, the commission has recommended that a specific amount be paid to any hospital that orders a scan regardless of whether they own the machine. This will focus the payments on those institutions that own and use the machine or those that purchase such tests from other sources. The amounts recommended by ProPAC are rather stringent and assume a machine is used to maximum efficiency.[5(pp 107-111)] The funds for this MRI add-on would be subtracted from the technology portion of the annual update amount. Critics of this approach argue that this is a major complication to the system and directly rewards only this one technology. While this may be true, we do have to face the much bigger issue that unless changes are made, the PPS approach could force medical equipment manufacturers to cut back substantially on research and development investments in quality enhancing but costly new medical devices and procedures. Some cutbacks may be appropriate but it is not clear that Congress wished to freeze our hospital care system with the technologies of the 1980s. Again, this is an issue that deserves much broader debate than it has received. How it is resolved could greatly affect both the efficiency of today's hospital system and the availability of new technologies for our future hospital system.

Conclusion

The Prospective Payment System, adopted by Medicare in 1982 to pay for inpatient hospital claims, is a radical departure from the retrospective cost-based system it replaced. The previous system, while modified several times, had been in place since 1965. The major difference between the two lies in the financial incentives they offer to hospitals once a person is admitted as an inpatient. The former system assured a hospital full payment for any approved service, test or day of care. The opposite is true for PPS. Once a patient is admitted and the likely DRG category is established the rate of payment is fixed. Any extra service, test or day of care adds expenses for the hospital but no additional revenue.

A related aspect of the new payment system is that changes in the way medical care is practiced do not automatically change the payment system. This is both a major advantage of the new system and a very significant challenge to those responsible for the ongoing operation of the program.

As might be expected, there are many critics of this new approach to paying hospitals. Some question its basic design and believe that it cannot succeed no matter how thoughtfully it adjusts to its perceived problems. They believe it is based on an inherently flawed approach. Others, myself included, believe that there are many very desirable aspects of PPS which, if appropriately modified, can form the basis of a long-term hospital payment system. Regardless of which camp a person is in, PPS is the law of the land and is not likely to be replaced in the immediate future. It is therefore incumbent on all of us to make it work better. By that, I mean it should pay hospitals in total at a level that reflects the attitude of all Americans as to the type and quality of the hospital system they want and are willing to pay for. It should also include the correct structural characteristics to assure that the individual patient receives the appropriate amount and type of care consistent with the cost of that care and the medical benefits it produces.

There are those who believe that PPS should be viewed as an interim, transitional system to some form of total capitated or Medicare voucher plan. While there is much to commend a capitation system and I believe the current capitation option for Medicare beneficiaries will continue to grow, I do not believe it is a panacea for all the problems raised by PPS. All our current knowledge about how capitated medical plans operate is within a total medical system that has been very liberally funded for new medical procedures and devices and that has sufficient funds from other sources to assure that the system has adequate backup capacity. Suppose all medical care in the United States was delivered by various forms of fixed capitated plans. Under this condition, could we be assured that our total health care system would receive adequate funds to provide the level and quality of medical care we want? And would such a system provide the right incentives to medical researchers and equipment manufacturers to invest in the research and development needed to keep the quality of our system at the level we want and are willing to pay for? I do not think we know the answers to these questions. Even worse, I don't even hear these questions being discussed!

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Competition Incentives—Smaller Carrot, Bigger Stick

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For years it was argued that "There is no price competition in health care" or "There is market failure in health care." One proposed solution to steadily growing costs was the establishment of marketplace competition, while another was rate regulation to control hospital expense increase.

The apparent quick success of statewide rate review systems has deceived some people into thinking that an immediate short-run dragging effect on rates of increase would have any long-run effect on the system and would substitute for competitive approaches.

Rate review won't work to downsize the health delivery system because it attempts to control only *supply* of care without any impact on *demand* for care. Both must be affected, but rate review has no effect on incentives for patients or physicians or on reducing demand for care.

Now we know that the major causes of those cost increases—first dollar coverage, cost-based reimbursement and third-party payment—were inherently inflationary by offering incentives for more providers to give more services to more patients, at ever-growing rates of increase in gross national (and state) expenditures for health care, and with ever-growing levels of cost-shifting to private sector payers. They were also inherently unrealistic since the consumer of care was shielded from its cost.

Rearranging the cost/payment structure, we know now, requires changing incentives for each element of the health care delivery system: physicians, hospitals and patients as well as payers. Incentives for controlling both supply and demand are necessary. Patients must be offered financial incentives to prevent the need for care through more healthy life-styles; to seek less costly care when they must, and to help pay for it so they will understand cost relationships. Physicians must be offered financial incentives to change medical care patterns of the past two decades that stressed high-tech science, specialty training and hospital-based equipment.

Physicians have always competed among themselves for patients and that competition can only intensify. But in a competitive system, physicians must compete not only against each other, but against hospitals, insurers, alternative delivery plans and government. Physicians are now competing in a system that not only awards them a smaller share of the money pie but that also yields them less professional satisfaction, less status and less and less control over their medical practices.

Incentives for hospitals in a competitive system stress more efficient management, reduced operating costs, marketing and planning for the future. Each of these characteristics is opposite to the incentives under cost-based reimbursement, which encouraged new programs, new staff, increasing technology and preserving the status quo balance of power between management and labor and between hospital management and the medical staff. In a cost-based world, the role of hospital trustees was partly ceremonial and partly business-like. In a competitive environment, trustees are placed at risk to be more effective.

Each health care payer—federal and state government, insurers, employers—has adopted a different approach to cost containment in the competitive environment. They differ in approach, but all agree on the need to shift costs and risks—to anyone possible as long as it is away from themselves. The Medicare Prospective Payment System has adopted two approaches toward shifting risks and costs. First, patients are assessed larger monthly premiums and new responsibility for sharing the cost of hospital bills. Second, payments based on diagnosis-related groups (DRGs) shift risks to hospitals. A DRG system has very clear targets: reduce the number of surgical procedures, shorten hospital lengths of stay and reduce utilization of ancillary services. The bulk of hospital cost increases has traditionally occurred because of great numbers of "little ticket" items rather than more widely publicized "big ticket" heart operations and the like. A DRG system will reduce the number of laboratory tests and x-ray studies and will offer incentives to care for patients in less costly settings—from inpatient to skilled nursing or to ambulatory or home care.

The Medicare Prospective Payment System (PPS), although installed hurriedly, was not invented without cause. After several failed attempts to contain medical costs, the federal government was faced with mounting budget deficits, two decades of increasing expenditures and the specter of a bankrupt Medicare Hospital Trust Fund. Trying to balance the competing and shifting demands for improved access,

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quality of care and cost containment rose to the top of the policy agenda. During these start-up years, the consequences of PPS and DRGs are now becoming known.

Whether the Medicare PPS is really "competitive" could be the subject of several other articles. But it is already clear that one of the global effects of DRG formulas is a redistribution of funds from region to region, state to state, rural to urban and hospital to hospital. But the operational consequences are also readily apparent:

- *Reductions* in admissions, patient days, length of stay, elective operations, physician income, tests, x-ray studies, ancillary services, nursing hours per patient, intensive care, total hospital employment, nurse employment, spread of technology, cash flow for rural and small urban hospitals, standing orders for presurgical workups, overnight stays for testing, access to care, cost-shifting to private payers.
- *Increases* in patient copayments and deductibles, accounts receivable, empty beds, acuity in inpatient settings, outpatient/ambulatory care, acuity in outpatient/ambulatory settings, interest in bioethical issues, uncompensated care, net revenues for some hospitals, demand for nursing home beds, "no-care zone" problems, home care by families, two or three "tier" care, hospital efficiencies, tighter review procedures, health maintenance organization growth, primary care gatekeeper systems.

It is gratifying to report that there is apparently no discernible difference in the high levels of care being delivered in hospitals by their dedicated medical staffs.

The US health system has delivered very high quality health care in the past and is continuing to do just that. Among the products of competitive forces are accusations of too short lengths of stay and too few resources expended. But few instances of problems from premature discharge of patients have been documented, and few examples of problems from readmissions have been proved. Yet, that was the whole point of installing market forces: to reduce both supply and demand for care, and to provide fewer services to inpatients and discharge them earlier.

There is a strong perception within elements of the hospital industry that competition in the delivery system and, in principle, the federal policy of prospective payment should be supported. Hospital leaders realize the fiscal and political realities and know that there will be no return to cost reimbursement. Given that attitude, the role, function and performance of the Prospective Payment Assessment Commission (ProPAC) deserve examination and evaluation.

The commission was appointed to propose technical adjustments to the Prospective Payment System. From our vantage point, that work has been accomplished on time, in a refreshingly nonpartisan manner favoring neither hospitals nor government. For the most part, ProPAC's conclusions have seemed reasonable and have received hospital industry support. In his excellent article in this issue, Stuart H. Altman, PhD, Chairman of ProPAC, has presented very clearly the thinking process of his group and the calculations underlying commission recommendations. Commission members accepted their mission in good faith and have attempted, to date, to act scientifically. They have been the voice of rationality in an irrational system. The Health Care Financing Administration (HCFA), however, has rejected almost all of the ProPAC recommendations, sometimes by publishing regulations before the commission has reported. Clearly, budget needs override all other consideration.

One area where ProPAC does command considerable respect is among congressional staff, even if commission recommendations are not enacted into law. ProPAC concepts can be seen filtering through, if not the actual numbers. The group has also received some criticism, particularly in justifying the calculation of its 2.2 % increase.

On the other side, HCFA is duplicating some of the effort by doing its own calculations, arriving at different conclusions which are opposed by both hospital interests and ProPAC.

These conflicts show only the initial tip of the incredibly complicated iceberg of a formula/numerical system such as DRGs. It makes capitation look easy. The incessant tinkering and technical adjustments will eventually fill a thick manual and lead to system overload.

As Altman said, PPS is here, good or bad. His back of the hand brush-off to vouchers is almost a non-sequitur at the end of the paper. He said it needed to be discussed. It does that, and I wish he would lead that exact discussion from his vantage point as a nonpartisan scientist. If ProPAC is to be effective, it will be exactly that independent role that will succeed. But, in the meantime, the system works backward. HCFA should propose issues for ProPAC to examine and report back. As it is now, ProPAC proposes and HCFA responds with a different agenda.

Special Article

Chronic Disease in a General Adult Population

Findings From the Rand Health Insurance Experiment

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Using questionnaire and physical screening examination data for a general population of 4,962 adults aged 18 to 61 years enrolled in the Rand Health Insurance Experiment, we calculated the prevalence of 13 chronic illnesses and assessed disease impact. Low-income men had a significantly higher prevalence of anemia, chronic airway disease and hearing impairment than their high-income counterparts, low-income women a higher prevalence of congestive heart failure, diabetes mellitus, hypertension, hearing impairment and vision impairment. Of our sample, 30% had one chronic condition and 16% had two or more. Several significant pairs or "clusters" of chronic illnesses were found. With few exceptions (diabetes, hypertension), the use of physician care in the previous year for a specific condition tended to be low. Disease impact (worry, activity restriction) was widespread but mild. Persons with angina, congestive heart failure, mild chronic joint disorders and peptic ulcer disease reported a greater impact than persons with other illnesses.

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Treating chronic disease presents an ever-increasing challenge to the medical community. As a consequence of progress in curing acute diseases, the emphasis in medicine has turned to long-term management of functional impairments associated with chronic conditions. We can assess the burden of chronic illness in many ways—epidemiologic, economic and psychologic. Despite extensive statistics on the incidence and prevalence of individual diseases, however,[1-13] we know little about the overall ramifications of chronic illnesses for a general population of nonelderly adults.

Chronic diseases can be defined as conditions that last more than three months; they encompass incurable diseases (such as osteoarthritis, hypertension), seasonal conditions (such as allergic rhinitis) and those that disappear and then "flare up" (peptic ulcer). They may appear singly or in combinations.[14,15] Among adults younger than 65 years, about 33% (or nearly 20 million persons) suffer from one or more chronic diseases that limit their function.[16,17] They are disproportionately poor and elderly; more than half face limitations in their major life activities (work, housework and so forth).[17-19]

The nation devotes 80% of its health resources to chronic disease.[20-26] "Indirect costs" in the form of earnings lost often exceed "direct costs" for medical treatment.[26] Persons with rheumatoid arthritis, for instance, earn 50% of the income they might otherwise have earned.[27]

Significant psychologic effects of chronic disease include concern about the disease itself, worry about not being able to carry on normal activities, anxiety about the loss of independence and loss of work and uncertainty about the cost of

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ABBREVIATIONS USED IN TEXT

CHF = congestive heart failure
COAD = chronic obstructive airway disease
HIE = [Rand] Health Insurance Experiment

treatment. For example, 63% of patients with rheumatoid arthritis in one study experienced a major change in their psychosocial status as a result of their disease.[28]

Little information in the clinical literature illuminates the chronic disease status of the general adult population. Here we combine information on the prevalence, associated effects and use of medical care for important chronic conditions or impairments in a sample of persons 18 to 61 years of age in the United States at the end of the 1970s.

Methods

The Rand Health Insurance Experiment

Data for this paper came from the Rand Health Insurance Experiment (HIE), a decade-long randomized controlled trial of the effects of alternative methods of financing health care services.[29,30] The HIE enrolled 7,706 persons in 2,756 families who participated from November 1974 to January 1982. They came from six sites—Dayton, Ohio; Seattle, Washington; Fitchburg/Leominster, Massachusetts; Franklin County, Massachusetts; Charleston, South Carolina, and Georgetown County, South Carolina—that represented urban and rural locations in the four US census regions. Excluded from the experiment were persons eligible for Medicare because of age or disabilities, persons eligible for care in the military medical system, persons indefinitely institutionalized (such as in prison) and families whose incomes exceeded $57,000 (the upper 3% of the income distribution in mid-1984 dollars). Except for these intentional differences, families were representative of the general population of the area where they resided.

We report on the experience with chronic disease of 4,962 adults (aged 18 to 61 years) up to the time they began their participation in the experiment.

Definitions of Health

Building on the World Health Organization definition of health,[31] we developed a broad set of health status measures covering several distinct categories[32]: general health (physical, mental and social health and general health perceptions), health habits and physiologic health (presence and impact of various chronic diseases). The physiologic dimension comprised 18 chronic or quasi-chronic "tracer" conditions that met several criteria[33-48]:*

- They are common.
- They can be defined concretely in terms with which most physicians would be comfortable.
- They can be measured easily and accurately with the tools available to the HIE.
- They can cause substantial discomfort, disability, morbidity or premature death.
- They are disorders for which appropriate medical care offers considerable symptom relief and control of physiologic status, if not outright cure.

Data Collection

During HIE enrollment, all adults completed a lengthy self-administered medical history questionnaire. The questionnaire contained more than 25 disease-specific batteries; each was introduced by a "skip" question (or set of questions) related to any physician diagnosis in the past or to the past or current presence of significant symptoms related to that illness. Persons who said they did not have a diagnosis or symptom of a particular disease skipped on to the next diagnosis-specific battery. Those who answered the skip question positively were instructed to complete the battery. The remainder of each battery asked about additional symptoms, recency of physician visits for the problem, prescription of and use of medications or other therapies for the condition, self-care practices and adverse effects such as worry or activity restriction that the person attributed to this particular illness (see Table 1).

A randomly selected 60% sample of all adults also took a multiphasic screening examination at which we obtained numerous physiologic measures (see Table 1). Many standard tests were done, such as common blood tests; others provided data specific to our needs, such as those related to arthritis. We asked questions regarding present health or recent drug use so we could properly interpret laboratory test results and avoid contraindicated examinations, such as chest x-ray films for pregnant women. No "hands-on" examination by a physician was done, neither was an invasive or potentially embarrassing procedure carried out.

For several conditions, we used more than one source of information to classify HIE participants. For instance, we determined which persons believed they had diabetes mellitus from responses to the physician-diagnosis question; we further classified them as having diabetes or not based on the use of insulin or oral hypoglycemic pills or serum glucose results. This multiplicity of data enabled us to estimate more accurately disease prevalence and to assess the degree to which people who had a condition were aware of and acknowledged that they had it.

Field experience in the first HIE site (Dayton) led us to revise the diagnosis-specific batteries, sometimes substantially. Thus, some results exclude Dayton. Some information is also reported by income status at enrollment (that is, upper and lower third of the family income distribution).

Reliability and Validity

Extensive analyses confirmed the reliability of our disease-specific measures. For all objective tests, test-retest (split-sample) reliabilities were high. Our disease prevalence rates approximated what might be expected in a general adult population, based on comparisons with data generated by the National Center for Health Statistics and specialized prevalence studies.[33-48] Slightly understating disease prevalence is possible, however, because we adopted conservative disease definitions acceptable to experts in the relevant medical specialities and because permanently disabled persons eligible for Medicare (less than 1% of the sample) and the aged were ineligible to participate in the study. We know, however, of no systematic bias in prevalence estimates owing to refusal of

*Apart from the authors of this article, the following persons were coauthors of one or more of the disease-specific monographs cited: Kenneth Applegate; Sjoerd Beck, MD; Daniel Berman, JD; Betsy Foxman, PhD; Marc Rosenthal; Randi Rubenstein; Bonnie Scott, MD, and John Zielske, MD.

persons to participate in the HIE; those who accepted and who refused the initial offer to join the study appear not to differ in any material way.[49]

Controlling for Age and Sex

Because chronic disease is more prevalent among older people and women, we should adjust for age and sex when

TABLE 1.—*Sample Questionnaire Items, Screening Examination Tests and Disease Definitions*

Chronic Condition	*Sample Questionnaire Item*	*Screening Examination Measure*	*Definition of Disease at Enrollment**
Anemia	In the past 12 mo, has a doctor prescribed any of these treatments for your anemia: special diet, iron pills or shots, vitamin pills or shots or blood transfusions?	Hemoglobin, hematocrit, erythrocyte count and other hematologic measures	Hemoglobin (grams/dl): <13.0, men 18 yr and older <11.5, women 18 yr and older <10.0, pregnant women
Angina pectoris	Have you had any discomfort, heaviness or pressure in your chest during the past 12 mo?	None	Angina probably present or present with mild or moderate impairment according to responses to series of questions about pain in specific locations in chest with or without exertion and use of nitroglycerin
Chronic obstructive airway disease, chronic bronchitis (CB) and chronic obstructive pulmonary disease (COPD)	During the past 3 mo, how much has your chronic bronchitis or emphysema worried or concerned you?	Pulmonary function tests: Forced vital capacity (FVC) Forced expiratory volume in 1 s (FEV_1)	CB: phlegm on most days for at least 3 mo of year, or MD diagnosis and use of breathing exercises or postural drainage COPD: FEV_1<75% of predicted, FEV_1/FVC ratio<80%, *and* has CB; FEV_1<75% of predicted, FEV_1/FVC ratio<80%, no CB, no CHF, dyspnea, history of smoking
Congestive heart failure (CHF)	Do you currently take diuretic pills for your condition?	Chest x-ray film	Combinations of responses to questions about use of heart medications, dypsnea at night, MD diagnosis, ankle edema, use of diuretics and dyspnea with little or no exertion
Diabetes mellitus	In the past 30 d, how many days did you actually check your urine at least once?	Postload blood glucose level	Taking insulin or oral antidiabetic agents; 2-h postload glucose>200 mg/dl; 2-h postload glucose level 160 to 199 mg/dl and MD diagnosis
Hay fever (current)	In the past 12 mo, did you get any shots to help prevent hay fever or other plant allergies?	None	Combinations of responses about past history, current symptoms and use of injections or medications
Hearing loss	Can you usually hear and understand what a person says, without seeing his face and without a hearing aid, if he whispers to you from across a quiet room?	Pure-tone audiometry	Average hearing threshold level without a hearing aid of 26 db or more
Hypercholesterolemia	When was the last time you saw a doctor about your high cholesterol?	Serum cholesterol level	Cholesterol level >300 mg/dl; taking anticholesterol drugs; cholesterol level 260 to 299 mg/dl *and* MD diagnosis or on diet
Hypertension	Has a doctor said that you had high blood pressure?	Blood pressure (BP)	BP <140/90 mmHg and taking BP drugs; BP 140/90 to 159/95 mmHg with or without medicines and MD diagnosis; BP >160/95 mmHg with or without medicines
Joint disorders (arthritis, gout)	How much of the time has the trouble with your joints or muscles kept you from doing the kinds of things other people your age do?	Grip strength, walking speed, joint size of fingers, serum rheumatoid factor, uric acid level	Pain, aching, swelling, stiffness in joints for as long as a month, or when touched, or upon getting out of bed and lasting 15 min or more; MD diagnosis of gout; positive rheumatoid factor test
Thyroid disease	Has a doctor ever said you had goiter or thyroid trouble?	Thyroid function tests: serum T_4 level, T_3 uptake, free T_4 index	Hypothyroid: Taking thyroid drugs; abnormally low free T_4 index Hyperthyroid: Taking thyroid drugs, abnormally high free T_4 index (and not pregnant or taking contraceptives); abnormally high serum T_4 level
Ulcer disease (active peptic ulcer disease)	In the past 3 mo, have you been troubled by episodes or attacks of stomach pain or stomachache (other than that caused by overeating)?	None	Previous MD diagnosis *and* taking antacids daily or recent and frequent episodes of stomach pain relieved by milk, occurring>1/2 h after eating or occurring at night
Functional far vision impairment	During the past 3 mo, how much of the time have eyesight problems kept you from doing the kinds of things other people your age do?	Visual acuity: without correction; with correction if available; pinhole acuity	Vision in one or both eyes, with correction if available, is worse than 20/20

MO = physician, mmHg = millimeters of mercury, T_3 = triiodothyronine, T_4 = thyroxine

*For more details on each condition, see references 33 to 48.

testing whether diseases are related to income or to each other. In this paper, we have used regression for adjustment. To investigate the effects of income on disease and the effects of having one disease on the probability of having another, we used logistic regression models with "dummy" variables for six sex-age subgroups (men and women; 18 to 34 years, 35 to 49 years, 50 to 61 years). For example, we used a logistic regression model to estimate the association between having congestive heart failure (in this case, the "dependent variable") and having chronic obstructive airway disease (the "explanatory variable"). The coefficient on income or on the explanatory disease is the measure of association, and the χ^2 statistic derived from the change in the likelihood ratio with that variable omitted is the measure of statistical significance; values of P less than .05 are taken as significant. Because the regression coefficient for disease A in predicting disease B is identical to the coefficient for disease B in predicting disease A, each pair of diseases was analyzed only once.[50]

Results

Sample

Of the 4,962 persons 18 to 61 years of age, just over half were women; more than a third had less than $10,660 and another third had more than $15,950 in family income adjusted for site and family size (mid-1984 dollars). The most common family configuration consisted of two adults 18 years or older and at least one child (47% of families); 18% of families consisted of just two adults.

Prevalence

Prevalence of individual chronic diseases. Hypertension, chronic obstructive airway disease (COAD), chronic mild joint disorders, anemia (among women), hay fever and far vision impairment were the most common chronic conditions in this adult population (Table 2). We observed significantly more joint disorders, anemia, congestive heart failure (CHF), thyroid disease (all $P < .001$) and angina ($P < .01$) among women than men and more COAD and hypertension (both $P < .001$) among men than women. All conditions except anemia and hay fever among women showed the expected positive association with age.

We were particularly interested in learning whether the prevalence of these chronic conditions differed by income group (low versus high income). Because income is confounded with age and sex, we tested whether income was significant in predicting the presence of each disease or impairment in regressions that controlled for age and sex. Across both sexes and all ages, low income was significantly related to the presence of COAD ($P < .05$), anemia and joint disorders (both $P < .01$), CHF, hearing impairment and functional far vision impairment (all $P < .001$). Income had no detectable relationship to the other illnesses studied. All the conditions significantly related to income were more likely to appear among the poor than the well-off.

To focus on the older age group, we show in Table 3 the rates by sex and income for persons aged 45 to 61 years. Except for hypercholesterolemia among men, again any conditions significantly related to income occurred more among the poor.

Severity of chronic conditions. Illness severity among persons whom we classified as having a disorder was generally mild for all conditions assessed by an objective physiologic measure. For example, among persons with hypertension (defined here as those with a measured diastolic blood pressure of greater than 90 mm of mercury), the mean diastolic blood pressure was 97.3 mm of mercury and the mean systolic blood pressure 171.2 mm of mercury. Among persons classified according to physiologic evidence, the level of severity was also mild for diabetes mellitus (mean glucose level, 247.8 mg per dl), anemia among women (mean hemoglobin level, 10.8 mg per dl) and hypercholesterolemia (mean serum cholesterol level, 290.1 mg per dl).

Prevalence of 'chronic illness.' The burden of chronic disease is not limited to the presence of a single condition in any given person. To determine how widespread "multiple" chronic disorders might be, we calculated the percentages in our adult sample with none, one and two or more major chronic conditions. We restricted these analyses to ten condi-

TABLE 2.—*Prevalence Rates Per 100 Men and Women of Selected Chronic Conditions by Sex and Age*

Chronic Condition or Impairment	Men			Women		
	Age Group, Yr			Age Group, Yr		
	Total 18 to 61	18 to 44	45 to 61	Total 18 to 61	18 to 44	45 to 61
Anemia	3.0	2.5	4.4	11.4	11.8	10.4
Angina	0.9	0.3	2.8	1.8	0.7	5.1
COAD*	13.5	12.6	17.0	8.4	8.0	9.5
Congestive heart failure	1.7	0.8	5.0	3.5	2.4	6.8
Diabetes	2.2	1.6	4.1	3.0	1.6	7.1
Hay fever	14.9	16.2	10.5	16.9	17.5	15.2
Hearing impairment	3.6	1.7	10.2	3.5	1.6	9.0
Hypercholesterolemia	5.2	3.7	10.5	4.6	1.6	13.2
Hypertension	16.2	11.1	33.4	11.1	4.3	31.4
Joint disorder	14.7	11.7	24.5	21.3	15.1	39.4
Thyroid disease	0.9	0.6	2.0	3.2	2.1	6.6
Ulcer disease	3.8	3.4	5.1	3.8	3.2	5.7
Vision impairment	16.4	12.9	27.9	22.1	17.2	36.9

COAD = chronic obstructive airway disease

*Persons 18 and 19 years of age are not included.

tions, excluding hay fever and vision and hearing impairments, to persons 20 years and older who received the enrollment screening examination and to those with valid data on all ten illnesses. (We adopted this age restriction because we considered the interpretation of spirometry results to be problematic for persons aged 14 to 19 years.) Overall, about 30% of persons 20 to 61 years of age had one chronic illness and an additional 16% had two or more (Table 4). Almost two fifths of the women aged 45 and older had two or more such problems.

Are there clusters of illness, or do illnesses occur independently? Some demographic groups, such as older women, are more likely to have certain of these illnesses, but even allowing for age and sex, certain illnesses may occur together more frequently than would be predicted by chance alone. In fact, the data in Table 4 show somewhat more clustering within the age-sex groups than expected ($P = .04$ based on a summed χ^2 test against the four Poisson distributions).

Table 5 shows which of the chronic diseases were significantly correlated (in pairs) after controlling for age and sex. The measure of association shown in the lower triangle of the table is the level of significance of the coefficient of the "explanatory variable" disease (such as COAD) in a logistic regression predicting the probability of occurrence of a "dependent variable" disease (such as CHF). Congestive heart failure is significantly associated with eight of the nine remaining chronic diseases; by contrast, anemia and thyroid disease are each associated with only two other conditions. One cluster consists of angina, CHF, COAD, joint disorders and ulcer disease; another cluster comprises CHF, high blood pressure, hypercholesterolemia, diabetes and possibly thyroid disorders.

What are the chances that an individual patient might have the second problem in one of these illness pairs if he or she already has the first? The chance of having an illness is usefully expressed in terms of the "odds," $P:(1-P)$, where P is

TABLE 3.—*Prevalence Rates of Chronic Conditions Per 100 Persons 45 to 61 Years by Sex and Income Tertile*

Chronic Condition or Impairment	Men		Women	
	Low Income	High Income	Low Income	High Income
Anemia	13*	2	14	11
Angina	5	2	6	5
COAD	29*	12	11	9
Congestive heart failure	6	3	10*	5
Diabetes	4	4	12*	4
Hay fever	9	10	14	14
Hearing impairment	18*	7	13*	6
Hypercholesterolemia	2	13†	14	10
Hypertension	37	31	38*	27
Joint disorders	22	25	42	37
Thyroid disease	2	2	6	6
Ulcer disease	4	4	5	5
Vision impairment	26	25	44*	28

COAO = chronic obstructive airway disease

*Significantly different from high income at $P < .05$.
†Significantly different from low income at $P < .05$.

TABLE 4.—*Men and Women With One, Two or More Selected Chronic Conditions by Age**

Count of Chronic Conditions†	Men		Women		Total
	20 to 44 Yr	45 to 61 Yr	20 to 44 Yr	45 to 61 Yr	
Sample, number	892	277	1,039	369	2,577
1 chronic condition, percent	27.8	36.8	28.2	32.8	29.6
2 or more conditions, percent	10.5	25.6	11.0	38.2	16.3

*Table includes only those enrollees who underwent the enrollment multiphasic screening examination, completed the medical history questionnaire and had valid data on all ten illnesses.
†Anemia, angina, chronic obstructive airway disease, congestive heart failure, diabetes mellitus, hypertension, hypercholesterolemia, joint disorders, peptic ulcer disease, thyroid disease.

TABLE 5.—*Associations Among Pairs of Chronic Conditions After Controlling for Age and Sex*†*

Chronic Conditions	Chronic Conditions									
	Anemia	Angina	COAD	CHF	Diabetes Mellitus	Hypercholesterolemia	Hypertension	Joint Disorders	Thyroid Disease	Ulcer Disease
Anemia	...	2.4		2.4						
Angina	‡	...	4.9	12.0				3.9		2.9
COAD		‡	...	5.1				2.4		2.6
Congestive heart failure (CHF)	§	‡	‡	...		4.0	2.8	3.6	2.8	3.6
Diabetes mellitus					...	2.6	2.3		3.8	
Hypercholesterolemia				‡	‡	...	2.5			
Hypertension				‡	‡	‡	...			
Joint disorders		‡	‡	‡				...		3.7
Thyroid disease				‡	‡				...	
Ulcer disease		§	§	‡				‡		...

COAO = chronic obstructive airway disease

*Each number represents the increased odds of one disease being present when a second disease is present, versus when the second disease is absent, based on a logistic regression that predicts the probability of occurrence of one disease in the presence of another after controlling for age and sex.
†Blank spaces mean that there was no significant association between the two conditions.
‡The association is significant at $P < .001$
§The association is significant at $P < .05$.

the probability of having the illness (as reflected in population prevalence rates). For instance, if the prevalence of a disorder such as angina is 2%, the odds a given patient will have it are 1:49 (.02/1 − .02 = .02/.98 = 1:49). Conversely, the probability corresponding to odds of x:y is given by $P = x/(x + y)$, so odds of 1:49 have a probability of 1/(49 + 1), or 1/50.

Building on the properties of odds and odds ratios, we show in the upper triangle of Table 5 (for the most highly related pairs) how much more likely people with a certain disease are to have another disease, controlling for age and sex. The values are the *change* in the odds of one disease being present when a second disease is present versus when the second disease is absent. From these numbers, we can estimate the probability that a person with one disorder will have a related condition by multiplying the odds of having only one of the diseases by the value shown in the table.

For example, if the prevalence of CHF in those without angina is 4%, the corresponding odds are .04/.96 = 1:24 in this group. The odds are 12 times as great, or 12:24, that a similar person with angina will have CHF; this translates into a probability of CHF in the presence of angina of 33% (12/[24 + 12]). Further, the prevalence of hypertension in the HIE population was roughly 12% and that of diabetes roughly 3%, giving odds of 12:88 and 3:97, respectively. If the "explanatory condition" is not too common, the prevalence of the "dependent condition" in the absence of the other condition is approximately the overall prevalence. Thus, the odds that a person with diabetes will have hypertension are 2.3*12:88 (about 24% prevalence among diabetic persons), and the odds of a person with hypertension having diabetes are 2.3*3:97 (almost 7% prevalence among hypertensive persons). For these "clusters," therefore, the risk of having one chronic disease when a certain other disease is present can be greatly increased even among a general adult population.

Awareness of and Use of Physician Care for Chronic Conditions

Undetected illness. By comparing screening test results with questionnaire information, we could estimate the degree to which people were aware of a particular problem or impairment that we eventually classified them as having. More detailed analyses reflected a considerable reservoir of undetected illness at the start of the study.[33–48] For instance, about half of the persons with hypercholesterolemia and with diabetes mellitus were unaware of their condition (based on physiologic measures of elevated levels of cholesterol and serum glucose, respectively), as were more than two thirds of persons with anemia (based on abnormally low hemoglobin levels). Finally, even though blood pressure checks are perhaps the easiest (being noninvasive) and most widespread of screening tools, almost three in ten adults apparently had no knowledge of their elevated blood pressures.

Use of physician care. For persons whom we classified as having a definite condition and who themselves claimed on the questionnaire to have the illness, we calculated the percentages of those who reported receiving medical care for that condition. Percentages of people with care in the previous year or currently under physician care (mainly within the previous three months) are given in Table 6.

Two thirds or more of the people classified as having CHF, diabetes, hypercholesterolemia, hypertension and thyroid disease had seen a physician for that specific problem within the previous year. Not surprisingly, patients with those same conditions had the highest percentages for being under current care. Less than a third of the relevant patient group had sought care in the preceding year for hay fever or hearing disorders. Less than a quarter of persons with anemia or peptic ulcer disease was under current care for those disorders and only about a tenth of those with hearing impairment had seen a physician recently for that problem.

TABLE 6.—*Persons With a Specific Condition Who Reported Receiving Physician Care in the Past Year or Within the Past 3 Months*

Chronic Condition or Other Illness	Condition Known to Patient, Number	Saw Physician Within Previous Year,* Percent	Currently Under Care, Percent
Anemia	140	48	24
Angina	70	46	31
Congestive heart failure	95†	66	41†
Diabetes	39	87	56
Hay fever	664†	27	12†
Hearing impairments	25	31	16
Hypercholesterolemia	62	72	37
Hypertension	220†	79	47†
Joint disorders	707†	39	18†
Thyroid disease	57	68	42
Ulcer disease	139†	42	19†

*All entries in this column are for non-Dayton sites only.
†Specified entries in these columns are for non-Dayton sites only.

Levels of reported compliance with physician prescriptions and therapeutic advice. Compliance with physician advice about therapy or self-care activities is an important element of management. We asked our sample about medications or other kinds of curative or preventive activities that their physicians might have recommended or prescribed and about the degree to which they followed their doctors' advice. Therapies and preventive measures can also be self-initiated, so in some cases we asked about the use of certain remedies or activities with or without a physician's advice.*

Physicians evidently advised the use of medications to manage hypertension and ulcer disease quite frequently (see column 2 of Table 7). Counseling for self-care activities among patients with diabetes was also commonly provided.

Compliance, reflected by the percentage of persons who said they currently used prescribed therapies, was in general high (see column 3 of Table 7), although in some cases this conclusion is based on a small number of people. Reported levels of compliance were higher for patients with diabetes, for those who had had iron or vitamin supplements (or both) prescribed for anemia and for patients who had had medications prescribed for hay fever, hypertension and hypercholesterolemia.

The last column of Table 7 shows the extent of reported use of these therapies among the entire group of persons who had one of these conditions, whether or not they had been so advised. For most conditions, the percentage of people using

*We did not ask directly pertinent questions for hearing impairment or vision impairment; the therapy questions for COAD refer mainly to people with symptoms of chronic bronchitis, not emphysema or chronic obstructive pulmonary disease. Medications are omitted from the thyroid disease and diabetes groups because the use of disease-specific drugs, such as insulin for diabetes, was important in defining the presence of those diseases.

a therapy on professional advice was larger than those using it in the absence of such advice. Although this is not surprising in the case of, say, medications for an elevated cholesterol level or high blood pressure, both of which require a physician's direct action, it is perhaps surprising for conditions such as hay fever.

Summary. Medical care for patients with chronic illness can be thought of as moving from a tree trunk to a twig, where the number of persons diagnosed as having a condition is reduced as one moves to branches concerning whether they are aware of their problem and, then, whether they seek care, obtain therapy and follow such therapeutic regimens. Following persons with hypertension illustrates this concept. About 70% of our hypertensive population knew about their high blood pressure; of this "aware" group, about 80% had sought care in the prior year and almost 50% had seen a physician in the preceding three months. Moreover, of the patients who knew they had hypertension, about 80% had been advised to take medications; of them, more than 90% complied. Thus, of the original group we classified as having elevated blood pressures, about a third had had recent care for their hypertension and about half were taking prescribed medications.

Levels of Disease Impact

We wanted a wide range of "outcome" measures for longitudinal analyses in the study. Some came directly from the physiologic measure characteristic of the illness—that is, blood pressure in hypertension—but we did not have analogous physiologic measures for every condition studied. To overcome this lack, we asked several standard "disease impact" questions of all persons who had, or believed they had, these various illnesses. We then calculated the percentages of persons who reported they had been worried or concerned about their illness in the recent past or who had had to restrict daily activities at least "a little of the time" specifically because of the disorder. All persons classified as having a condition were analyzed. For respondents who were unaware of having an illness and who thus would not have been asked the disease impact questions, we imputed an answer of "none."

Nearly every one of the ten major chronic conditions occasioned a good deal of mental distress (Table 8). Problems associated with symptoms such as pain (ulcer disease, joint disorders, angina) or shortness of breath (congestive heart failure) prompted more worry and concern than did "symptomless" disorders (such as the mild anemia or hypercholesterolemia seen in our population). Worry about these illnesses was quite extensive but mild. Among persons reporting any worry or concern, the median level was only "a little" except for CHF and diabetes, for which the median level was "some" worry.

Generally, people were less likely to restrict their activi-

TABLE 7.—*Extent of Use of Medications, Therapies or Self-Care Activities Among Persons Reporting a Chronic Illness*

Condition and Therapy	*1 Condition Known to Patient, Number*	*2 Patients Who Were Advised to Use Specific Therapy, Percent*	*3 Patients Who Followed Advice, Percent*	*4 Patients in Column 1 Who Used Specific Therapy Whether or Not Advised, Percent*
Anemia	140			
Diet		6	44	6
Iron pills/shots		56	86	77
Vitamins		18	92	31
Blood transfusions		4	33	2
Congestive heart failure	95*			
Diuretics		40	79	32
Diabetes mellitus	39			
Keep feet clean		64	100	95
Cut toenails straight		62	88	77
Not walk barefoot		56	73	56
Not wear tight hose		59	91	67
Watch weight		85	79	70
Hay fever	738			
Medications		31	87	33
Hypercholesterolemia	62			
Medications		27	71	21
Diet		NA†	NA	50
Hypertension	273			
Medications		81	91	74
Use less salt		51	49‡	20
Thyroid disease	57			
Surgical procedure		18	NA	68
Irradiation		12	NA	NA
Ulcer disease	139*			
Medications		75	NA	NA

*Non-Dayton sites only.
†NA = Relevant question not asked.
‡In all, 49% reported never adding salt to food at the table; 10% reported never adding salt at the table *and* never adding or having salt added to their cooking.

ties because of these chronic conditions (see Table 8) than they were to express worry and concern. The same four diseases that ranked high for causing worry and concern also ranked high for limiting ordinary activities: CHF, chronic joint disorders, peptic ulcer disease and angina. For almost half of all the chronic disorders (CHF, angina, hypercholesterolemia, hearing loss and diabetes), the median period of activity restriction among those persons who reported any was "some of the time."

Discussion

We have reported on 13 conditions that are of major concern to those primary care physicians whose patient population consists mainly of adults. We found that in a general adult population up to late middle age, a considerable portion of its members are afflicted with one or more chronic conditions—some serious and some not so serious—that impinge negatively on their lives. For example, prevalence rates ranged from about 19% for mild joint disorders to almost 2% for angina pectoris. Strong associations with age were detected for most chronic conditions.

Chronic illness occurred somewhat more frequently among poorer adults after controlling for age; this was especially true of hearing and vision defects, anemia, COAD, CHF and joint disorders. We cannot tell whether low income is a cause or a result of these problems, but both explanations are plausible.

About 16% of our adult sample had two or more (of ten) chronic conditions. In addition, we found that the "relative odds" of several chronic illnesses conditional on having another were very high, even when we controlled for age and sex. Some of these associations were expected (the strong connection between CHF and angina); others, such as joint disorders and ulcer disease, may be less commonly observed in ordinary medical practice but may warrant further investigation. Undetected illness was appreciable for some of the conditions we studied.

Few, if any, published data are available on the average amount of care sought by people with the chronic conditions we studied. Thus, although the medical profession may well have "norms" or expectations about the desirable frequency of physician visits for persons with, say, elevated cholesterol levels or vision impairments, we know little about whether the average patient observes those norms. In 1975 about three quarters of the US population aged 15 to 64 years had visited a physician at least once in the preceding year.[51] By that benchmark, the rate of care-seeking in the year before the study began specifically for chronic conditions that our participants knew they had seems rather low; it was by no means excessive. Of course, our respondents could have visited a physician for other problems; whether this was so and whether the specific chronic condition might have been indirectly evaluated at such visits would not be reported in the disease-specific questionnaires.

Only for diabetes, hypertension and hypercholesterolemia did the percentage of people who saw a physician in the previous year approach the benchmark cited above. Patients with some conditions, such as chronic joint problems, angina or peptic ulcer disease, arguably ought to have at least annual follow-up; our reported rates of care-seeking for these disorders fell considerably below this standard, especially if biases related to underreporting and overreporting of medical care utilization were to be taken into account.[52] These crude "diagnosis-specific visit rates" are consistent with the view that physician care for these conditions was not being oversupplied.

The degree to which patients followed their physician's advice and counsel was high but not obviously related to the seriousness of the condition. An appreciable proportion of persons who had (and knew they had) diabetes, hypertension and hypercholesterolemia reported that they followed their physicians' recommendations, but so did those with hay fever. We did not verify the accuracy of these compliance self-reports; some respondents may well have overstated their adherence to a given medical regimen. Compliance with drug regimens for acute or chronic conditions is not easy to measure in large population surveys[53] and may well differ by the type of drug; one account puts overall drug compliance among persons with hypertension at just under 60%.[54] Nonetheless, we interpret our figures as reflecting an impressive degree of adherence to professional advice, at least about remedies or self-care activities that patients comprehend are directly related to their illnesses.

Our simple measures of the impact of specific diseases on people's lives suggest that anxiety about specific chronic illnesses is widespread but mild. Whether this implies that Americans are oversensitive about their health or that they are showing a growing sophistication about health may be largely a matter of individual interpretation. Persons with angina, CHF, joint disorders and ulcer disease tended to report more disease impact (worry and concern and activity limitations) than those with the other conditions studied.

In summary, dealing effectively with chronic disease requires a multifaceted approach. Most chronic disease in a general population is mild, but a considerable amount is undiagnosed. Efforts must be made to ensure that those who need regular care receive it, especially when the burden of chronic disease falls disproportionately on persons of low income. Finally, even mild chronic illness imparts considerable anx-

TABLE 8.—*Adults Reporting Worry and Concern or Restricted Activity, by Chronic Condition*

Chronic Condition	Persons with Condition,* Number	Reported Worry or Concern, Percent	Reported Activity Restriction, Percent
Anemia	215	22	9
Angina	70	76	46
COAD	298	50	13
Congestive heart failure	131	86	71
Diabetes mellitus	74	31	16
Hay fever	738	59	26
Hearing impairment	101	6	10
Hypercholesterolemia	148	14	7
Hypertension	384	38	12
Joint disorders	903	77	41
Thyroid disease	62	19	3
Ulcer disease	190	86	45
Vision impairment	560	47	15

COAD = chronic obstructive airway disease

*Sample includes all persons whom we eventually classified as having the disease. Those who said they did not have the condition—even though we had so classified them on the basis of other data—and who thus did not answer the question are included in the denominator and considered to have responded "no" to these questions.

iety about one's health. Effective care requires physicians to cope with this aspect of chronic disease even as they attempt to control its physiologic manifestations.

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Special Article

Pediatrician Participation in Medicaid—Findings of a Five-Year-Follow-up Study in California and Elsewhere

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Medi-Cal—California's Medicaid program—underwent significant changes during the period 1978 through 1983. Most notable were the imposition of new copayments, reductions in physician reimbursement and selective contracting for hospital services. The state-funded medically indigent program was transferred to the counties and the state began to experiment with bulk purchasing of drugs and supplies, a lock-in for overutilizers and primary care case management.

How have these changes affected primary care providers' participation in Medi-Cal? Surveys of California pediatricians in 1978 and 1983 suggest that while most continue to participate, the level of limited participation in Medi-Cal increased from 23% to 51%. Most pediatricians express discontent with the level of Medicaid payments and there is a growing sentiment that Medicaid regulations interfere with the provision of high quality medical care. Future Medi-Cal policy developments, such as contracting for physician services, should be structured in ways that maximize participation of primary care providers in the program.

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During the early 1980s the federal government and many state governments began to reconsider their capacity and willingness to finance health care for the poor. The major impetus for this development was growing health care costs. Other related developments included fiscal pressures during a period of economic slowdown, widespread concern about taxes and public spending, the thrust of the "New Federalism" toward increasing the state role in public policy, concern with both long-term reform and short-term budget reduction in health care cost containment and a new willingness to subject health care to the forces of price competition.[1,2]

Nowhere were these developments more evident than in California. California's state revenues are usually well above expenditures and per capita spending exceeds the national average. But state Proposition 13 in 1978 and the more recent federal Medicaid budget reductions put significant pressure on the state budget. California's Medicaid program (Medi-Cal) is the country's largest: 3,747,880 people received Medi-Cal in 1982, making up 18% of total US recipients. Medi-Cal expenditures grew from $2.4 billion in 1978 to $3.6 billion in 1983. With rising program costs and state budget pressures, the emphasis of Medi-Cal policy changes between 1978 and 1983 was cost containment. This period saw particular reliance on utilization controls and heightened price competition among California's many health care providers to control Medicaid's costs.

Nationally, spiraling health care costs led to the Medicaid provisions included in the Omnibus Budget Reconciliation Act of 1981 (OBRA) and the Tax Equity and Fiscal Responsibility Act of 1982 (TEFRA). This federal legislation increased the fiscal pressure on state budgets by reducing the federal matching payments to the states for their Medicaid expenditures—by 3% in 1982, 4% in 1983 and 4.5% in 1984. In addition, it required Medicaid program reductions in eligibility and covered services, and gave states new policy options for Medicaid cost containment.

Efforts are currently under way to evaluate the impact of OBRA, TEFRA and other Reagan era health policy changes on health care costs. There is also concern, however, that these changes in Medicaid and the health care environment

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ABBREVIATIONS USED IN TEXT

IPA = independent practice association
OBRA = Omnibus Budget Reconciliation Act of 1981
PPO = preferred provider organization
TEFRA = Tax Equity and Fiscal Responsibility Act of 1982

may have eroded earlier gains in the access of the poor to health care.[3] Physician participation in Medicaid is a critical determinant of access to health care for the poor: when office-based physicians do not participate, patients must either rely on hospital emergency rooms, outpatient clinics or free-standing emergency rooms, where care may be relatively more expensive, or perhaps forgo care altogether.[4] Previous research has shown that Medicaid program characteristics affect physician willingness to accept Medicaid patients[5-7]; thus it is reasonable to hypothesize that recent policy developments have influenced Medicaid participation in California.

This paper examines the influence of recent Medi-Cal policy developments on the participation of California's pediatricians in the program. First, we describe changes in Medi-Cal policies between 1978 and 1983 in the areas of eligibility, covered services, reimbursement and cost containment. Second, we present data from 1978 and 1983 surveys of pediatricians concerning their Medicaid participation, comparing the responses of California pediatricians with those of pediatricians in other states. Finally, we analyze recent trends in pediatricians' Medi-Cal participation in the context of changes in the states' socioeconomic and health care policy environment, concluding with recommendations for fostering greater Medi-Cal participation among California pediatricians.

Research Methods

Information about physicians and their experiences with state Medicaid programs was collected in surveys conducted by the American Academy of Pediatrics in 1978 and 1983.[5] Since Medicaid policies vary widely by state and are expected to differ in their impact on physicians, states with differing Medicaid policy characteristics were chosen for a 1978 study of the impact of Medicaid policy on physician participation in the program. The 50 Medicaid programs were placed in four categories based on their 1975 scores on an index of Medicaid reimbursement levels and an index of other state Medicaid program attributes such as restrictiveness of eligibility and service provisions.[5] Thirteen study states were chosen randomly from the four categories. It was particularly important that several large states be included in the study because just a few large states account for most of the nation's Medicaid eligibles and expenditures. Thus, the probability of a state's selection was weighted by the number of pediatricians in the state. The study states chosen by this method are shown in Table 1. The same 13 states were included in a 1983 follow-up study.

A random sample of nonfederal, office-based physicians, distributed approximately equally across the 13 states, was selected from self-designated pediatricians included in the American Medical Association's masterfile (see Table 1). In the 1978 study, personal interviews were conducted with 814 physicians for an overall survey response rate of 92.6%. The 1978 response rate for California pediatricians was 93.5%.

Pediatricians surveyed in 1983 included the panel of 814 respondents from the 1978 study. While there was some attrition due to factors such as retirement and death, all but four of the panel physicians were located. A supplementary sample of pediatricians entering practice since 1978 was added to ensure that the age distribution of physicians surveyed in 1983 was representative of the pediatrician population. Survey data for 1983 were weighted to reflect the age distribution of office-based pediatricians in each state. A total of 791 pediatricians completed the 1983 questionnaire for an overall response rate of 79.7%. Overall response rates for the panel and the supplementary sample of new physicians were 83.7% and 71.9%, respectively; for California pediatricians response rates were somewhat lower at 71.1% and 60.0%, respectively. The state sample sizes for 1983 are shown in Table 1. Demographic characteristics of the pediatricians surveyed in 1978 and 1983 are shown in Table 2.

The pediatrician surveys included questions about the physician's practice characteristics and experiences with Medicaid as well as with the new alternative practice arrangements—for example, independent practice associations (IPAs) and preferred provider organizations (PPOs)—that have become more prevalent in recent years. Physicians were asked specifically if they accepted all, some or none of the Medicaid and non-Medicaid patients that contact them, and what proportion of their patient load was Medicaid. The measures of Medicaid participation are constructed from these items. Physicians were also asked to provide some information about fees and reimbursements, and to rate the importance of some commonly identified problems with the Medicaid program.

TABLE 1.—*State and Pediatrician Samples, 1978 and 1983*

State	State Sample Size 1978	1983
California	58	56
Colorado	53	55
Georgia	97	91
Indiana	77	71
Iowa	37	37
Maryland	64	64
Massachusetts	63	70
Nebraska	27	28
New York	54	53
Oklahoma	58	57
Pennsylvania	63	54
Tennessee	84	81
Texas	79	74
Total	814	791

TABLE 2.—*Description of the Sample*

Physicians Surveyed	California 1978	1983	Total All 13 States 1978	1983
Physicians surveyed, number	57	56	814	791
Sex, percent				
Male	91.4	91.1	89.8	88.1
Female	8.6	8.9	10.2	11.9
Board certified, percent	77.6	77.9	72.7	79.5
Foreign medical school graduates, percent	13.8	14.6	12.8	11.6

Data describing state Medicaid policies and economic, political and social conditions were gathered from secondary sources and verified by state Medicaid personnel. Changes in state Medicaid eligibility and covered services between 1978 and 1983 were identified using various publications which describe state Medicaid programs.[8-10] The analyses that follow also incorporate state socioeconomic information from the Census Bureau, the Bureau of Labor Statistics and the Department of Health and Human Services Office of Family Assistance.[11,12]

Highlights of Medi-Cal Policy Developments, 1978-1983

Overview

Our review of Medi-Cal policies during the period between 1978 and 1983 indicates many substantial program changes. Overall, the state did not initiate drastic eligibility reductions. Rather, various forms of utilization controls were initiated. In addition, several very fundamental changes were made in the state's strategy for reimbursing Medicaid providers. These changes are described below.

Medi-Cal Eligibility

As noted earlier, California's Medicaid program is the nation's largest, making up 18% of all US recipients. The program is broad in its eligibility provisions, covering much of California's poverty population. An estimated 39% of poor children were not covered by Medicaid in 1980, which compares favorably with the national average of 52%.[13]

OBRA mandatory provisions restricting eligibility were implemented gradually in late 1981 and early 1982; approximately 50,000 children lost eligibility because of these cuts.[12] Few other eligibility reductions were undertaken at the state's initiative, however. Notable exceptions were the transfer of responsibility for medically indigent adults to the counties and reduction of the medically needy program, which provides Medicaid benefits to families not qualifying for welfare. "Medically needy" families become eligible for Medicaid by "spending down" to a certain level by deducting medical expenses from their incomes. In California in 1983 this protected income level was $601 per month for a family of four; it had been reduced from $801 per month the previous year.

Medi-Cal Services

In addition to the eight federally mandated services, California provides 27 optional services. Several have been added since 1978. Also during this period the state began to experiment with primary care case management systems and home and community-based services on a demonstration basis. Economic efficiencies were sought through bulk purchasing of certain drugs and medical equipment.

In 1982 the state began limiting use of certain optional services to two occasions of service per month. Several other important steps were taken to control use of Medicaid services. These included a "lock-in" program restricting overutilizers to one pharmacy or one physician. In addition, the state began to require copayments for certain services and categories of recipients. For example, a $5 copayment was imposed on nonemergency care received in emergency rooms for all recipients except children younger than 12 years and women receiving prenatal care.

Medi-Cal Reimbursement

The most notable changes in Medi-Cal policies between 1978 and 1983 affected the reimbursement of providers.

TABLE 3.—*Overview of Participation*

Participating Pediatricians	*California* 1978 Percent	*California* 1983 Percent	*Total All 13 States* 1978 Percent	*Total All 13 States* 1983 Percent
Pediatricians who have ever participated in Medicaid	98.3	97.3	94.2	93.0*
Pediatricians who currently participate in Medicaid	98.2	91.4	85.1	82.0†
Average patient load covered by Medicaid (participants only)	32.5	24.3	15.7	14.7
Participants who limit participation in Medicaid	22.5	51.3‡	26.0	35.0‡

*$P < .10$.
†$P < .05$.
‡$P < .01$.

TABLE 4.—*Pediatrician Attitudes About Problems With the Medicaid Program*

Problems With the Medicaid Program as Evaluated by Respondents— % Rating Each of the Following as "Very Important":	*California* 1978	*California* 1983	*Total All 13 States* 1978	*Total All 13 States* 1983
Not all health care services are covered by Medicaid	28.6	31.7	26.1	31.0*
It takes too long to complete the necessary paperwork	43.1	36.0	33.7	35.8
It takes too long to receive payment from Medicaid	48.3	35.4	24.1	34.8
Medicaid program regulations are too complex	43.1	45.6	38.6	46.3†
Medicaid payments are too low	66.1	78.8	59.7	66.5†
Medicaid payments are too unpredictable	50.0	60.4	41.3	52.4†
Medicaid program regulations interfere with providing high quality medical care	25.9	43.5	29.4	32.8
Problems such as broken appointments and language barriers make it difficult to treat Medicaid patients	46.6	44.4	29.0	31.1
The type of patient who is eligible for Medicaid	...	19.4	...	14.8
There are few Medicaid eligibles in this area	...	2.7	...	5.0

*$P < .05$.
†$P < .01$.

First, in 1982, there was a 10% reduction in the level of physician reimbursement under the state's fee schedule, the California Relative Value Scale. Second, the basis of hospital reimbursement underwent several changes between 1978 and 1982 and, finally, in 1982 Medi-Cal began reimbursing hospitals based on selective contracting.[14,15] In areas where selective contracting was implemented, only those hospitals entering into an agreement with Medi-Cal were eligible to receive reimbursement. Payment to contracting hospitals is based on an all-inclusive negotiated daily rate.

Pediatrician Medi-Cal Participation: Survey Results

Pediatrician participation in Medi-Cal declined somewhat between 1978 and 1983 (see Table 3). The proportion of pediatricians reporting Medicaid participation fell from 98% to 91% between 1978 and 1983, a change that is very close to statistical significance. Despite the decline, however, the 1983 participation level is higher than the level for all 13 states.

Like other measures of Medicaid participation, the average percentage of patient load covered by Medicaid decreased, from 33% in 1978 to 24% in 1983, although this change was not statistically significant. Of California's original 1978 panel of physicians, 85% reported fewer Medicaid patients in their practices in 1983. California ranked first among the 13 states in the average Medicaid patient load in both 1978 and 1983.

While most California pediatricians continue to participate in Medicaid, a dramatic increase occurred in the proportion of California pediatricians choosing to limit Medicaid participation (see Table 3). These "limited participants" have room in their practices for additional patients but still choose not to accept all Medicaid patients who contact them. The level of limited participation increased from 23% in 1978 to 51% in 1983. California ranked third among the 13 states in the percentage of limited participation, surpassed only by Georgia and Pennsylvania.

Table 4 shows pediatricians' responses to questions about problems they experience with Medi-Cal. In both 1978 and 1983 the majority of pediatricians reported dissatisfaction with Medi-Cal payment levels, a problem shared with pediatricians surveyed in the other 12 states. Paperwork and bureaucratic complexity are also judged to be substantial problems by most California pediatricians in both 1978 and 1983. By comparison, these problems increased significantly in importance between 1978 and 1983 for the combined sample of pediatricians in all 13 states. The most significant change in attitudes among California's pediatricians is the growing sentiment that Medi-Cal regulations interfere with the provision of high quality medical care. Only 26% of California's participants identified this interference as very important in 1978 while 44% identified it as such in 1983.

One apparent explanation for decreased Medi-Cal participation in California is the widening discrepancy between physician fees and the program's reimbursement. Some of this discrepancy is undoubtedly due to the 10% reimbursement reduction implemented in California in 1982. Table 5 indicates the 1978 and 1983 self-reported physician fees and reimbursement levels for a well-child visit and for a medical follow-up visit. In 1978 the average Medicaid reimbursement for a well-child office visit covered 74% of a pediatrician's usual fee. The ratio dropped significantly by 1983 to 64%. The discrepancy is even wider for follow-up medical visits, for which physicians received 75% of their usual fee in 1978 and only 56% in 1983. Comparison with other states in the study supports the interpretation that Medicaid reimbursement affects participation: in general, states that have maintained high levels of participation (such as Iowa and Colorado), or have raised their participation levels (such as Tennessee), are those that have high or improving reimbursement relative to usual fees. Multivariate analyses of the total sample support this interpretation as well.[5,16]

Another reason for declining participation in Medi-Cal may be the bureaucratic complexity faced by pediatricians seeking reimbursement for services rendered to Medi-Cal patients. Our survey asked pediatricians to provide estimates for several indicators of the program's administrative perfor-

TABLE 5.—*Pediatrician Fees and Medicaid Reimbursement*

	California		Total All 13 States	
Pediatric Office Visits	*1978*	*1983*	*1978*	*1983*
Well-child office visit				
Average current usual fee	$21.90	$30.20	$16.63	$22.72
Average Medicaid reimbursement	16.30	19.20	11.81	15.85
Follow-up medical visit				
Average current usual fee	16.90	23.30	13.05	17.69
Average Medicaid reimbursement	12.60	13.00	9.83	12.65

TABLE 6.—*Medi-Cal Administration*

	California		Total All 13 States	
Medicaid Paperwork	*1978*	*1983*	*1978*	*1983*
Average % of Medicaid claims returned for additional work	11.0	19.0†	12.9	15.0*
Average number of weeks for Medicaid to make payment	8.1	8.0	7.2	6.5†
Average number of minutes to fill out a Medicaid form	7.5	8.7	7.3	6.9

*$P < .10$.
†$P < .05$.

mance such as the proportion of claims returned to the physicians' office for additional work after initial submission for reimbursement, the length of time between billing and payment and the time needed to complete a Medicaid claim. Table 6 indicates that in 1983 pediatricians report significantly more returned claims than in 1978. Other indicators of the program's administrative performance have remained unchanged.

In summary, pediatricians are troubled by Medi-Cal's declining reimbursement levels and increasing bureaucratic complexity. In addition, they are increasingly concerned that Medi-Cal regulations interfere with the provision of high quality medical care. Most pediatricians continued to participate in Medi-Cal between 1978 and 1983, with participants on average reporting Medi-Cal patients to be almost one quarter of their patient load. Significantly more California pediatricians, however, are finding it necessary to limit their Medicaid participation, perhaps in response to declining reimbursement, increased administrative overhead and dissatisfaction with other program regulations.

Discussion

Extraordinary changes have taken place in the delivery of health care in California during the last seven years, foreshadowing developments likely to occur in other states in the coming years. For this reason, it is important that the consequences of these changes be analyzed fully. Some of these changes involve Medi-Cal providers and patients only indirectly. These include the growing number of health care providers in California, the new incentives to reduce lengths of stay in hospital created by the Medicare prospective payment system and the evolution of alternative nonhospital delivery systems such as IPAs and PPOs that are negotiating discounted rates to provide care to the patients of California's private insurance carriers.

Other changes have affected Medi-Cal providers and patients more directly. Most notable is the implementation of selective contracting, which has redistributed Medi-Cal dollars and patients among California's hospitals on the basis of price competition. In comparison with this fundamental restructuring of Medi-Cal reimbursement, Medi-Cal eligibility and services changed only slightly between 1978 and 1983. Despite recent budget pressures, California's children have generally continued to enjoy the benefits of a Medicaid program that extends broad eligibility and services. The important question in California is not so much whether a poor child will be eligible to receive needed services in that 61% of California's low-income children are covered by the program. Rather, the important question is where that care is likely to be available.

Pediatrician unwillingness to participate in Medi-Cal increased between 1978 and 1983, with dramatic increases in those limiting their participation. Recent reductions in Medi-Cal reimbursement levels probably account in part for the increasing dissatisfaction with the program. Indeed, in 1983 nearly 79% of California pediatricians reported that low Medi-Cal payments were a very important problem—up from 66% in 1978 and well above the total for pediatricians in all 13 states.

Private insurer contracting for the provision of nonhospital care may also be discouraging physicians from continuing to participate in Medi-Cal. Faced with increased competition, pediatricians are joining the ranks of the new IPAs and PPOs in order to enhance their advantage in the privately insured market.[14] In the scramble for market share, primary care providers appear to be limiting their commitment to publicly financed patients.

The prospect of state contracting for nonhospital Medi-Cal services may also be discouraging pediatrician participation in the program, especially since many California pediatricians are participating in the very IPAs and PPOs most likely to bid for Medi-Cal contracts in the future. However, California's primary care physicians have sustained Medi-Cal fee schedule reductions in recent years and may not accept further reductions in reimbursement. Competitive pressures may not be sufficient to force certain IPAs and PPOs into the Medi-Cal bidding, and the result would be a dramatically altered distribution of California's poor children among Medi-Cal providers in the future. In the process, the current access of Medi-Cal children to health care could be seriously compromised. Moreover, to the extent that these children must obtain primary care in hospital-based settings, the costs may be unnecessarily high.

Primary care physicians (whose office-based services are generally less expensive than those of outpatient departments and emergency rooms) might be attracted into state-initiated contractual arrangements both in California and elsewhere. If children are to have access to primary care in physicians' offices, however, state Medicaid programs will need to foster Medicaid participation. Our research suggests that states will need to preserve adequate reimbursement levels—whether capitation-based or fee-for-service. In addition, efforts need to be made to minimize paperwork associated with billing state Medicaid programs and to address the perception of physicians that Medicaid regulations interfere with the provision of high quality medical care to low-income patients.

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Forum

The Aim of American Medicine Within the Constraints of Today's Society

Beginning in the August 1986 issue the editors of *The Western Journal of Medicine* began a forum for dialogue and discussion of the aim and purpose of medicine within the constraints now being placed on health care. Readers and others are invited to submit their views constructively and succinctly. As many as space permits will be published in future issues of the journal. At an appropriate time all the material will be collated and, if possible, the distillate will be prepared as a statement on "The Aim of American Medicine Within the Constraints of Today's Society."

MSMW

Be a Pilot, Not a Pirate

LAURENS P. WHITE, MD

In *The Pirates of Penzance* Gilbert and Sullivan create some tension and a lot of humor by having the Nurserymaid, who is hard of hearing, make the mistake of apprenticing the young lad to a Pirate, instead of a Pilot. It is my aim, within the constraints of a short piece, to try to convince you to be a Pilot.

Professor David Stafford-Clark has suggested that the role of physicians in dealing with dying patients should be that of ships' pilots, guiding the patient through narrows or shallows, or in or out of dock. He emphasizes that the patient was the captain, who was responsible for the voyage, but who needed help at the beginning and the end, and occasionally in between. The pilot has his own journey, and can't go on the trips of others, but his job is to help others in their ships when they need help.

Our aim, as physicians, is and has been to practice the best medicine we can. For the past 40 years this has been, increasingly, good technical medicine, and we have, increasingly, ignored the human condition, instructed and accustomed as we are to treating the disease, not the patient. We bought the illusion that all we needed to do was to treat the lab value, the x-ray, the disease—and the human condition would take care of itself. Through this period our departments of pediatrics, medicine and surgery were taken over by biochemists and biophysicists who valued knowledge of enzymes highly, knowledge of feelings and needs little or not at all. Students got the message that the road to their salvation was through intermediary metabolism, which they studied and learned, and not through learning to care for and deal with a sick person, which they neglected. Marvelous scientific advances occurred via this emphasis. (A previous generation of professors, who were just as interested in chemistry and research, carried their humanity and love of people into their bedside teaching.)

Sam Standard, a wise old surgeon, quoted his patient Karen Blixen as telling him "When I'm with you I feel I am in loving arms." (She had no particular pleasure in his knowledge of the Embden-Meyerhof pathway.) We, as physicians, need to communicate our ability to love and understand every bit as much as to sell our technical skills. Patients expect more from physicians than they do from other health care workers, and to us they give up more of their independence. Most patients are aware of the severe limitations of the knowledge of a chiropractor, and come to such a person with limited expectations. Expecting little, they give up little independence to such a person. They count more on us. Curiously, what is expected is not only the technical things but more of our concern, of caring, of being able and objective in helping them through their difficulties, of being a pilot on their journey. They want a person who can take charge, when that is needed, and who can then let go. Physicians/pilots aren't needed for the entire trip.

Modern society is more and more critical of physicians, of our incomes and our behavior. We physicians are in pain because of a bizarre dilemma: as we know more and more and can perform greater and more complicated scientific wonders, we are coming under increasing criticism and are liked and respected less all the time. At least part of our failure must be our failure to reassure or convince people that we care for them. In part our problem stems from not having learned that behavior patterns that work well in acute, time-limited illness are maladaptive for treating patients with chronic illness. Part of our diminishing status may come from the helplessness and dependence that illness forces upon people, and from the resentment by sick persons toward those upon whom they have become dependent. The increasing hostility that we see in our patients may be, at least in part, a reaction to this feeling of depression and helplessness; a change in our concept of our role as physicians may diminish the anger and hostility we face from patients. In this sense we need to be willing to take charge during acute problems, give support and reasonable options for patient choice in the care of long-term illness and be concerned about maximum freedom the rest of the time.

As pilots we need all our technical skills to help the vessel

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through the trouble spots. As human beings we should try to limit these technical aspects of our job, and increase our human ability to deal with both the captain and with the crew. We need to delight in and honor our role as pilots, who leave the ship as it reaches the open sea. We can be called back if we are needed, but we have our own journey to take and we want it to be in freedom.

Medicine in the Future

JOHN L. KELTNER, MD

As we look to the future of medicine, it might serve us well to review the past. Certainly it is well known that history tends to repeat itself and the excellent book *The Social Transformation of American Medicine*[1] by Paul Starr emphasized this message. Many efforts have been made to develop governmental controlled socialized medicine. However, this has failed for many reasons which include the tremendous cost associated with government-run bureaucracies and the public's desire for independent free choice in a health-care system. Government's obligation to provide health care for the indigent and the poor resulted in the Medicare and Medicaid legislation of the 1960s. However, the tremendous cost associated with Medicare and Medicaid prevented further socialized programs from being developed.

The escalating costs of health care was one reason corporate America entered the health care system and, as Paul Starr relates in the last chapter of his book, we are presently in the era of the corporate takeover of American medicine. This has created several problems for modern medicine. Corporate America thrives on competition and, now that advertising is permissible, advertising and "marketing" have become the latest innovations to take place in modern medicine. However, the problem of ethics with advertising and marketing is producing tremendous difficulties for physicians today. We are defining new standards for the future, whether we like it or not, regarding what are ethical and unethical advertising. It has yet to be defined what these two standards really are, but clearly they will need to be spelled out if we are to continue to hold public confidence in our profession. Ethical advertising would be, one hopes, information transfer with public service in mind while keeping the promotion of self-serving needs of the individual or the institution to a minimum. Unethical advertising would be the use of the media to promote untrue or overstated claims about abilities or treatment options provided by an individual or institution. Clearly new standards in the fields of advertising and marketing for medicine will need to be defined. All medical advertising does not need to be bad, and if the public benefits by being better informed about their health and the potential services available to them, then all of society will be benefitted.

Cost containment is certainly an essential ingredient for medicine in the future. As pointed out by Beverly Myers in her article "Corporate Profits or Public Good"[2] in the August issue, the poor may suffer as corporate America takes over medicine. I would contend that there are three major problem areas that will suffer if corporate America takes over medicine without careful planning for them. The first is the care of indigent patients, who are already being squeezed out of the marketplace as private hospitals attempt to sign up HMO groups, PPO groups or other corporate centers. One way to take care of indigent patients would be to have each county foot the cost and care of indigent patients among all its hospitals and physicians on a proportionate basis. Thus, if there are ten hospitals in a community, each hospital would be responsible for providing 10% of the care for indigent patients. This would prevent the old "county hospital" or "city hospital" problems and would continue to provide quality care at hospitals that are maintained by corporate medicine but with high quality of care standards. The second problem area is research into the treatment and prevention of a variety of diseases—work which may suffer seriously as government bows out from subsidizing medical research. James C. Abegglen and George Stalk, Jr, in their book *Kaisha, The Japanese Corporation,* relate that in Japan the manufacturing industry finances almost all research and development that it performs and that the Japanese government finances limited research. With the corporate take-over of American medicine, it is also corporate America's obligation to be much more involved in sponsoring research into the treatment and prevention of devastating illness. Because corporations will benefit from new science which develops drugs, medical devices and surgically related material, they should fund a much larger portion of medical research dollars.[3] And third is the problem of who will provide the funds for teaching future generations of doctors if corporate America takes over without some type of governmental assistance for education. While we appear to have a doctor glut at present, without careful planning and if there is continued loss of funds for the training of future health practitioners we could be in serious difficulties in the future. Thus, the care of the indigent, research into the prevention and treatment of disease and the teaching of our future health-care practitioners must be carefully factored into the future corporate takeover of American medicine. Undoubtedly the government will continue to have to play a major role in financing these three major health care functions in the future.

As pointed out in James O. Mason's article "Medicine's Aims, Society's Constraints,"[4] prevention of disease through better education of the public should be the major thrust of future medicine. Clearly we have a generation of "video junkies" who gain many of their views and attitudes through television, whether we like it or not. If nearly 65% of the years of potential loss of life before age 65 is preventable, we need to have a constant barrage of TV informational items every Saturday morning, for example, informing our young minds about the potential risks of drugs, smoking and alcohol, and the potential benefits of proper diet, exercise and rest. Joseph A. Califano, Jr, in *America's Health Care Revolution,* calls smoking "slow motion suicide," a menace which he states has taken more American lives than all our wars and all our auto accidents combined, and, in addition, that "alcohol is a grim reaper involved in five of the ten leading causes of untimely death in America."[5] Thus, it is hoped that if we can educate a new generation about the hazards of

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abusing one's body, we may achieve a fundamental goal of medicine: preventing disease rather than attempting to cure it.

I believe the way to preserve the private practice of medicine with freedom of choice for all patients is to strengthen the preferred provider organization concept. While HMOs have been successful in some areas, they have never completely taken over medicine because patients still find that HMOs often are run in a bureaucratic fashion and limit freedom of choice which is inherent in the American public's desire. Preferred provider organizations which maintain the private practice of medicine at a reduced cost are perhaps the best way to keep this freedom of choice and to preserve the private practice of medicine for the future.

Information transfer will clearly be one of the major tasks in the future of American Medicine. Future physicians will continue to receive some continuing education through the printed word but computer interaction as well as video educational systems will have become integral parts of the medical education process. Compact laser disks will help to store information about patients and diagnoses, making far more information accessible to practitioners than ever before.

Finally, "The Essence of Being a Physician"[6] by Jacob Needleman stated the problem well for the training of modern physicians. A patient's need for compassion and humane attention will never be diminished by scientific technology. In fact, it will be necessary for all physicians to continue to practice the art of medicine by "compassionate engagement in the suffering of our fellowman." People have always cared for people and machines have never cared for people; this will not change with any future scientific advances.

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Medicine Is a Humanity

E. R. W. FOX, MD

As I READ the series of articles in the August issue on the aim of American medicine, written by skilled essayists, I was struck by their consensus: Medicine is in big trouble. We doctors are no longer loved.

Commercialization has taken us over. The Four Horsemen of big business, big government, the big insurance complex and the big hospital industry have not only put constraints on traditional medical care, but they threaten to render such care obsolete.

With the advent of technology it is predicted that the medical doctor is to become a technician, a mere extension of the machine. These authors are saying that specialists and subspecialists will be the doctors of tomorrow, and that primary physicians—the FP, the GP, the OB/GYN, the internist—will sink to the level of the "barefoot doctors," triage agents. Bioethicist Jonsen asks the rhetorical question: "Should physicians serve [only] as gatekeepers into the house of care?"

One author (not a physician) suggests that the adoption of a "national health program" would be a move in a desirable direction. Yet, in almost the same breath he acknowledges the inefficiency of government medicine and the inequities of socialized medicine.

Nowhere in the group of essays do we find the positive, definitive answer. We are left with a feeling of anger, frustration, even desperation—it seems there is not much we can do about it.

Let me step fearlessly into this void and state my contention that, yes, there is something we can do about it. We can say to the Four Horsemen, "Don't forget we are doctors of medicine concerned primarily with the care of our patients. And remember that in caring for our patients we determine how this nation spends 10% of its gross national product."

We will go on to say, "Yes, we admit we have become too involved in the mercenary side of the practice of medicine—but you forced that upon us. Now in an effort to regain our respectability, we, the quarter million American doctors, will propose to assume a Ghandi-like posture, as we sit on our collective posteriors, waging a nonviolent protest against the Four Horsemen's threats, and we will plead with organized medicine to do the same.

"We confess that, owing to the constraints foisted upon us by technology and by the commercialism and the litigiousness of our society, we may have lost touch with the human side of medicine. We regret this and we agree that it is time for us to renew our dedication to the sensitive care and understanding of the minds as well as the bodies of our patients. Forsaking the pursuit of the dollar, we are ready and eager to return to the Art of medicine.

"We can, therefore, enthusiastically join the trend now being followed by many of our medical schools, Harvard, the University of Washington, Utah, Mount Sinai School of Medicine, among others, encouraging a return to the study of literature and all the other humanities, for in those studies we find the emotional, psychological and cultural underpinnings of human behavior."

Barbara Berg, professor of medicine and literature at Mount Sinai, said it so well in describing the nature of the course being given to their students, "Dying, disease, anguish, pain, birth, hope, courage, love—these, the absolute substance of literary work are also the integral aspects of medical work."

And so, Four Horsemen, we will abstain from counting dollars, and return to the arts, music, painting, writing and perchance even poetry. William Carlos Williams wrote these words in his book *Doctor's Stories*:

> When they ask me, as of late they frequently do, how I have for so many years continued an interest in medicine and the poem, I reply that they amount for me to nearly the same thing.

Dr Fox is in private practice in Coeur d'Alene, Idaho, and is Special Editor for Idaho.

Refer to: Fox ERW: Medicine is a humanity, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Oct; 145:553-554

If we are willing to accept this commitment to the humanities, then, once again we will be looked upon as "cultured doctors," rather than greedy businessmen. Once again we will be members of an esteemed profession. Plenty of coins will still jingle in our pockets, and we will be happier. The medical profession will be restored to its pedestal, and doctors will again be loved.

The Healthiest Little Community in the United States

THOMAS L. PETTY, MD

THE FIRST SIGN he saw as he approached the little town said "Slow Down and Enjoy." His foot had already relaxed its hold on the gas pedal when he saw the second, "Welcome to the Healthiest Little Community in the United States." As he pulled into town he noted a clean, tidy little town snuggled away in the Arkansas River Valley. The tennis courts and jogging paths were noticeable as he pulled into a filling station in the main business district. After a fill-up and rest stop, he walked across the street for lunch. "You get really hungry driving cross country," he thought. He asked for the no-smoking section, "please," and the waitress said, "Sit any place you like, sir, this is a no-smoking community." He was curious about that comment when he sat down but he noticed that no one in this busy restaurant at lunchtime was smoking at all. There were no ashtrays.

The menu was interesting. Quite a variety of fish and chicken entrees, and a vegetarian plate was featured. The salt and cholesterol content on every item was listed. He figured that the 380 tasty calories he ate, a meal high in fiber, would probably last him to the next town where he planned to spend the evening.

As he was paying the bill he remarked about the trim, active people who he had seen walking up and down the street and the general attitude of healthiness that prevailed. "Your hospital must not do much business," he said to the manager. "Oh, our hospital closed five years ago because, I guess, we really didn't need it. We kept part of it for a nursing home for our old folks. There are more and more of them moving to this part of the country because of the clean air and tranquil life-style. The kids have everything organized, have entertainment and plenty to do. Some of the old folks are learning to fish for the first time in their lives."

The traveler was astonished. Here was a community where no one smoked and cigarettes were not even for sale. The town had decided it would be best if kids never started smoking. Everyone was active, either working or playing. Almost no one was overweight and everyone seemed to enjoy the atmosphere of health.

"We turned the other half of the hospital into a health promotion center," the manager went on. "People get their blood measured, checks for cancer and a lung capacity test. There is plenty of sunshine in the valley so we use a lot of sun screen. If anyone has sugar diabetes, we find that out. Eye checks for glaucoma and tests for blood where it shouldn't be are done up there by the volunteers."

The visitor got back in his car, buckled his seat belt and drove slowly out of town. "I guess this *is* the healthiest community in the United States! I wonder how they did it."

Dr Petty is Director, Webb-Waring Lung Institute, University of Colorado Health Sciences Center, Denver.

Refer to: Petty TL: The healthiest little community in the United States, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Oct; 145:554

Commentary

A Dream Trip to Australia

E. R. W. FOX, MD, *Coeur d'Alene, Idaho*

Perhaps if there had been a course in Bioethics 101 when I attended medical school, I would have promptly solved the problem presented to me by my friend Sam's hope of a dream trip to Australia. But in that distant medical school day, the word "bioethics" had not been coined, nor had we heard about those subspecialists called "ethicists."

Back in the 1940s the ethics of medical practice consisted mainly of not splitting fees and not enticing away our colleagues' patients. Of course, on our graduation day we saluted the Oath of Hippocrates, albeit with some reservations, knowing that we might someday have to "cut for stone," or that we might even be required one day to terminate an intrauterine pregnancy under certain anguishing circumstances.

Therefore, without the advantage of a formal course on ethics, I had only my experience to guide me in arriving at the right decision in the dilemma confronting my long-time friend and patient.

Sam and his wife Martha could boast of almost 40 years of good marital companionship. Theirs had been a happy life together. If there was one small cloud of unhappiness in their relationship, it was Martha's lingering homesickness for her native Australia.

As a 12-year-old girl, Martha had been torn from her playmates, her school and her childhood memories when her parents immigrated to the United States in search of financial advancement. Although she grew up to be a proud American citizen, throughout her married life she longed for a return visit to her homeland.

With this in mind, they planned and saved toward what was to be a memorable month-long vacation "down under." Their son and daughter joined in their enthusiasm. Each year at Christmas and on birthdays they would send gifts of money to swell the dream trip fund. Then, at long last, dates were set, tickets were purchased, reservations made. In four short months, Sam and Martha would be on their way.

Then disaster struck: Martha suffered a massive cerebral hemorrhage and died.

Sam was distraught and deeply depressed. Without Martha the future was empty. Life no longer seemed worth living. The dream of a trip to Australia had ended in an ugly nightmare.

Weeks passed and the deadline for cancellations approached. But when Sam announced to the children that he planned to give it all up, they rebuked him, saying, "Dad, we have given this a lot of thought and we have come to the conclusion that Mom would have wanted you to go. You should do this in memory of our mother."

A period of anguished soul-searching followed. Sam was finally able to agree that he could serve as Martha's surrogate by making this pilgrimage to the land of her birth. Whereas for a time during his depression Sam had doubted that life was worth living, even contemplating suicide, now his enthusiasm gradually returned, and once again he had a purpose in life. He was ready and eager to go.

The children suggested that in preparation for the trip, he should have his annual physical examination, even though it was not yet due. But here the plot thickens. Now we come to the ethical conundrum.

During the examination, the physician discovered a cancer, a malignant lesion of a serious type, but amenable to treatment. As I read the pathologist's report, I was distressed, even angry. How could Fate allow this to happen to my friend and patient at such a critical time, just when it seemed that a few rays of sunshine were coming back into Sam's life?

And why should I, as Sam's physician, be backed into the compromising position of having to choose one of several painful courses to follow? Knowing how much this dream trip to Australia meant to Sam and to his family, should I risk throwing my patient back into a deep depression by telling him he has cancer, and that he must give up his trip in order to undergo treatment?

Or should I indulge in a white lie, allowing Sam to go on his trip, planning to start treatment on his return? Perhaps I could inform only the son and daughter, letting them share the burden.

Or should I carry the whole load myself, saying nothing to anyone at this time, and hope the cancer will remain dormant until Sam's return?

Thinking only of ethical issues, putting aside all legal considerations, how could this troubled doctor arrive at the *one* right answer? Our hospital's medical staff has hard and fast protocols for every clinical contingency, but none for this frustrating ethical puzzle.

Where might I turn? Our ethics committee might help, but my patient is scheduled to leave the day after tomorrow. Moreover, that committee, like most committees, would provide as many answers as there are members.

No, the choice is up to me. I can only hope my decision will be the right one.

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A Survey of Hospital Privileges for California Family Physicians

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MOST STUDIES that have examined hospital privileges used by family physicians have surveyed hospital administrators[1-4] or family practice residency directors.[5-7] In only two national studies were practicing family physicians actually surveyed.[8-11] Stern and co-workers studied family practice residency program graduates who were also diplomates of the American Board of Family Practice.[8,9,11] In 1980 Clinton and associates examined the hospital practice privileges of nonfederal, office-based physicians who were active members of the American Academy of Family Physicians.[10]

This is the first survey of all active members of the California Academy of Family Physicians (CAFP). A total of 3,494 family physicians were mailed surveys in August 1984 and in June 1985. The survey was designed to evaluate hospital privileges granted to California family physicians and included the areas of obstetrics (routine delivery, complicated delivery, high-risk patients and cesarean section), general surgery (assisting, intermediate privileges and major privileges), intensive care (coronary care unit, intensive care unit and respiratory care unit) and newborn care. The physicians were also asked to state why they did not have specific privileges in their hospital practices. Reasons given for not using privileges included the following: privileges were not desired, privileges were denied, malpractice costs were prohibitive, there was no hospital service—for instance, obstetrics—and privileges would not be granted. Other practice-related information and demographic data on the physicians were also collected.

Method

In August of 1984, a self-administered questionnaire was mailed to all active members of the California Academy of Family Physicians. A second mailing in June 1985 was sent to all nonrespondents of the first mailing and to all members enrolled between August 1984 and May 1985. Names and addresses were obtained from the American Academy of Family Physicians. A total of 2,172 responses was received for a 62% response rate. This response rate compares favorably with other mailed questionnaire surveys.[12]

(Werblun MN, Kurata J, Nogawa A: A survey of hospital privileges for California family physicians. West J Med 1986 Oct; 145:556-558)

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Survey respondents were similar to the total CAFP membership in both age and sex. Comparing the percentages of respondents in the age categories with the percentages of CAFP members in those categories yields a Pearson correlation coefficient equal to 0.99, an extremely strong relationship. (The correlation between respondents and nonrespondents is 0.98). The average age of the respondents was 49 years for men and 40 years for women. The male-female distributions for respondents and the CAFP population are identical—91% male, 9% female). Due to these similarities, the results reported herein may be considered representative of the CAFP membership as a whole.

Results

Results were compared with those of the Pacific region (Alaska, Washington, Oregon, California and Hawaii) and the total US findings as reported by Clinton and colleagues. Differences between the California and the US percentages are similar to those found between the Pacific region and the United States in the study by Clinton and co-workers.[10]

Obstetric and Surgical Privileges

In Table 1 the results of this study and those of the study by Clinton and associates are compared for obstetric and surgery hospital privileges.

Fewer California physicians than Pacific region or US physicians indicate the use of obstetric privileges. About 26% of California physicians include routine obstetric care and delivery in their hospital practices; routine obstetric care and delivery privileges were used by about a third of both Pacific region and US family physicians. In comparison, ten years ago a survey of the California Academy of Family Physician members found between 21% and 40% of the physicians—depending on years in practice—included obstetrics in their practices.[13] Percentages for the other obstetric privilege categories are about half the Pacific rates as reported by Clinton and colleagues.[10] Overall, the Pacific region percentages are similar to those for the nation though slightly lower for three of the four obstetric privilege categories.

Fewer California physicians than Pacific region physicians reported using surgery privileges. More California physicians, however, assist in surgery than family physicians elsewhere in the United States. The privileges of surgery, "intermediate" and "major," for California physicians are lower than the national figures. Pacific region physicians reported a higher usage of surgery privileges than did family physicians elsewhere in the nation—up to 27% higher in the case of surgery assisting.

Hospital Privileges and Prohibitive Malpractice Insurance Costs

In Table 2 the results of this study are compared with those of Clinton and co-workers for obstetric and surgery privileges "not used" due to malpractice insurance costs.

Malpractice cost is given as the reason for not obtaining

obstetric hospital privileges by similar percentages of California and Pacific region physicians. These rates are at least twice the national rates.

Fewer California than Pacific region physicians cited malpractice insurance costs as the reason for not including surgery in their hospital practices. Both California and Pacific rates have similar patterns of relationship with the national rates. In California today and the Pacific region four years ago, the percentage of physicians not requesting surgical-assisting privileges because of prohibitive malpractice insurance costs is lower than that in the United States overall. It is higher, however, for the more involved surgical categories. In fact, the percentage of Pacific region physicians who do not include intermediate and major surgery in their hospital practices because of malpractice insurance costs is almost double that for all US physicians.

Hospital Privileges Used by Family Physicians

Surgery assisting was the most commonly used hospital practice privilege (see Table 3). In all, 74% of the respondents indicated that they included this in their inpatient hospital practices. Newborn care was the next most common privilege at 66%. The least used privileges were for complicated obstetrics, cesarean section, high-risk obstetrics and major surgery. Nearly 54% of the respondents reported coronary and intensive care unit privileges. Privileges in respiratory care units were reported by 30% of the respondents. An additional 23% included these intensive care privileges in their hospital practices, but only with consultation.

Practice Patterns of California Family Physicians

About 91% of the respondents practice full-time. Male physicians surveyed have been in practice longer than the female respondents—an average of 19.4 years as compared with 9.9 years. In addition, 46% of all respondents were in solo practice, 28% practiced with other family physicians and 13% belonged to multispecialty groups, with 2% in urgent-care practices. About 89% of the physicians had practices that included inpatient hospital care. Of the 260 physicians (14%) who reported having difficulty obtaining hospital privileges, 259 were able to obtain some privileges.

Educational Background of California Family Physicians

Of the responding physicians, 28% indicated family practice residency training; of these, almost 90% were younger than 45 years of age.

Discussion

This is the first survey of the California family physician population. Based on more than 2,000 physicians responding from a population of almost 3,500, it provides an accurate picture of the current hospital privilege situation for California family physicians. Most of the responding physicians (89%) had practices that included hospital care. Physicians were active in a variety of privilege areas (Table 3). Data from this survey and others demonstrate the importance of the family physician's role in hospital-based care.[4,8,9,14]

Overall, the findings of our study and those of others in the literature are very similar. The differences that were found are most likely due to differences in survey design—that is, surveying administrators versus physicians; time periods of surveys—the survey by Clinton and associates took place in 1980, ours in 1984-1985, and region surveyed.

Table 2 shows that these changes in practice patterns for obstetrics and surgery are not explained by increases in malpractice insurance costs since 1980. For both obstetric and surgery privileges, the percentages of California physicians

TABLE 1.—*Obstetric and Surgery Privileges in California, the Pacific Region and the United States**

Hospital Privileges	California, 1984-1985 (N=2,172), Percent	Pacific, 1980 (N=515), Percent	United States, 1980 (N=4,366), Percent
Obstetrics			
Routine	25.5	35.6	36.7
Complicated	7.8	18.1	20.6
High risk	5.2	10.5	15.1
Cesarean section	7.3	15.8	13.2
Surgery			
Assisting	74.3	82.4	55.5
Intermediate	24.1	44.4	32.5
Major	7.3	17.2	14.2

*From Clinton et al.[10]

TABLE 2.—*Obstetric and Surgery Privileges Not Used Due to Malpractice Insurance Costs for California, the Pacific Region and the United States**

Hospital Privileges	California, 1984-1985 (N=2,172), Percent	Pacific, 1980 (N=515), Percent	United States, 1980 (N=4,366), Percent
Obstetrics			
Routine	13.8	14.1	4.8
Complicated	10.4	11.0	4.0
High risk	10.0	10.8	4.1
Cesarean section	8.6	9.6	4.1
Surgery			
Assisting	1.3	2.4	3.4
Intermediate	5.6	9.1	4.7
Major	5.8	9.4	5.2

*From Clinton et al.[10]

TABLE 3.—*Hospital Privileges Used by Family Physicians in California, N=2,172*

Clinical Area	Family Physicians, Percent	Only With Consultation, Percent
Surgery assisting	74	3
Surgery, intermediate	24	5
Surgery, major	7	3
Coronary care unit	54	23
Intensive care unit	54	23
Respiratory care unit	30	23
Obstetrics, routine care and delivery	26	1
Obstetrics, complicated delivery	8	14
Obstetrics, high risk	5	11
Cesarean sections	7	5
Newborn care	66	2
Fractures	44	13
Psychiatry	31	15
Other	16	1

who do not include these in their hospital practices due to malpractice insurance costs are below the Pacific region percentages of four years ago.

A continued decline in obstetric services provided by family physicians and a decline in services provided by obstetrician-gynecologists due to malpractice insurance costs in this state will require legislative changes to protect the needs of the public.

Hospital administrators and trustees should recognize the high level of activity in hospitals by family physicians and adopt a positive attitude toward the establishment of departments of family medicine that have parity with other medical staff clinical departments.

Further studies would enhance the ability of hospital administrators and family physicians to interpret and implement policy regarding hospital privileges. Surveys should be repeated periodically to examine time trends in California family physicians' hospital privilege usage. A complementary study would be to survey California hospital administrators so that comparisons could then be made between physicians' perceptions of the availability of hospital privileges and those of administrators. If there are differences between physician and administration perceptions of privileges available, ways to resolve these differences would need to be considered. In addition, a new national survey is needed to determine if regional differences in hospital privileges are still as Clinton and co-workers reported them, or if there have been changes over time.

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In Memoriam

California Medical Association

BAY, MAX WILLIAM, Los Angeles. Died July 1984, aged 80. Graduate of University of California, San Francisco, School of Medicine, 1928. Licensed in California in 1928. Dr Bay was a member of the Los Angeles County Medical Association.

❦

BECKSTRAND, GRANT H., Palos Verdes Estates. Died January 30, 1986, aged 84 years. Graduate of Columbia University, New York, 1929. Licensed in California in 1935. Dr Beckstrand was a member of the Los Angeles County Medical Association.

❦

BERGMANN, ERNEST F., Atwater. Dicd in 1985, aged 69 years. Graduate of University of California, Irvine, 1962. Dr Bergmann was a member of the Merced-Mariposa Medical Society.

❦

BOUCHER, LUIS A., San Francisco. Died January 1, 1986, aged 49 years. Graduate of University of Alberta, Edmonton, Alberta, Canada, 1962. Licensed in California in 1969. Dr Boucher was a member of the San Francisco Medical Society.

❦

CHANDLER, WILLARD J. M., Irvine. Died January 12, 1986, aged 76. Graduate of University of Nebraska, 1937. Dr Chandler was a member of the Los Angeles County Medical Association.

❦

CHASE, MALCOLM S., Indio. Died June 5, 1986, aged 68. Graduate of the University of Virginia School of Medicine, Charlottesville, 1948. Licensed in California in 1960. Dr Chase was a member of the Riverside County Medical Society.

❦

CHASMAN, PAUL, San Bernardino. Died May 16, 1986, aged 61. Graduate of Indiana University School of Medicine, Bloomington, 1946. Licensed in California in 1962. Dr Chasman was a member of the San Bernardino County Medical Society

❦

COON, GEORGE W., Corona Del Mar. Died May 28, 1986, aged 88. Graduate of Rush Medical College, Chicago, 1922. Licensed in California in 1930. Dr Coon was a member of the Riverside County Medical Association.

❦

DAHLEEN, HENRY C., San Jose. Died May 15, 1986, aged 71. Graduate of Stanford University School of Medicine, Stanford, 1940. Licensed in California in 1940. Dr Dahleen was a member of the Santa Clara County Medical Society.

❦

DOYLE, JOHN P., Burlingame. Died July 9, 1986, aged 64. Graduate of St Louis University School of Medicine, St Louis, 1947. Licensed in California in 1950. Dr Doyle was a member of the San Mateo County Medical Society.

❦

FERREIRA, ANTONIO J., Los Gatos. Died May 19, 1986, aged 62. Graduate of Faculty of Sciences, Lisbon, Portugal, 1946. Licensed in California in 1954. Dr Ferreira was a member of the Santa Clara County Medical Society.

FINOCCHIARO, CIRINO, Pasadena. Died December 4, 1985, aged 82 years. Graduate of Creighton University School of Medicine, Omaha, 1928. Licensed in California in 1930. Dr Finocchiaro was a member of the Los Angeles County Medical Association.

❦

FRIEDMAN, DAVID B., Los Angeles. Died November 1, 1985, aged 69. Graduate of University of Michigan, 1940. Licensed in California in 1946. Dr Friedman was a member of the Los Angeles County Medical Association.

❦

GLENN, LAVERNE P., Anchorage, Alaska. Died April 27, 1986, aged 83. Graduate of Creighton University School of Medicine, Omaha, 1934. Licensed in California in 1934. Dr Glenn was a member of the Sacramento-El Dorado Medical Society.

❦

HARING, ROBERT P., Bakersfield. Died May 29, 1986, aged 77. Graduate of College of Osteopathic Physicians and Surgeons, 1935, and University of California, Irvine, School of Medicine, 1962. Licensed in California in 1935. Dr Haring was a member of the Kern County Medical Society.

❦

HARR, RALPH V., Santa Rosa. Died May 27, 1986, aged 83. Graduate of University of Michigan Medical School, 1927. Licensed in California in 1928. Dr Harr was a member of the Sonoma County Medical Association.

❦

HOOVER, BRYAN R., Los Olivos. Died December 17, 1985, aged 87. Graduate of Loma Linda University School of Medicine, 1935. Dr Hoover was a member of the Los Angeles County Medical Association.

❦

IRELAND, ROBERT M., Beverly Hills. Died November 1985, aged 75. Graduate of University of Southern California, 1940. Licensed in California in 1940. Dr Ireland was a member of the Los Angeles County Medical Association.

❦

JACOBSON, DOUGLAS R., Menlo Park. Died September 27, 1985, aged 45. Graduate of University of Chicago, Pritzker School of Medicine, 1965. Dr Jacobson was a member of the Santa Clara County Medical Society.

❦

KALLER, ROBERT G., Long Beach. Died January 23, 1986, aged 68. Graduate of Medical College of Wisconsin, Milwaukee, 1942. Licensed in California in 1943. Dr Kaller was a member of the Los Angeles County Medical Association.

❦

LAUGHLIN, THOMAS J., North Hollywood. Died October 7, 1985, aged 82. Graduate of Rush University, Chicago, 1933. Licensed in California in 1933. Dr Laughlin was a member of the Los Angeles County Medical Association.

❦

LEIVERS, ALFRED EMERY, Chico. Died May 18, 1986, aged 78. Graduate of Stanford University School of Medicine, 1938. Licensed in California in 1938. Dr Leivers was a member of the Butte-Glenn Medical Society.

LORCH, SIEGFRIED, Glendale. Died December 31, 1985, aged 92. Graduate of J. W. Goethe University, Germany, 1920. Licensed in California in 1941. Dr Lorch was a member of the Los Angeles County Medical Association.

❦

MCCARTY, EUGENE, Fresno. Died May 31, 1986, aged 45. Graduate of University of California, Irvine, School of Medicine, 1968. Dr McCarty was a member of the Fresno-Madera Medical Society.

❦

MOORE, MILLARD PHIL, Porterville. Died May 11, 1986, aged 79. Graduate of California College of Medicine, Irvine, 1962. Licensed in California in 1945. Dr Moore was a member of the Tulare County Medical Society.

❦

MOYLE, CHESTER ARTHUR, Merced. Died September 13, 1985, aged 92. Graduate of University of California, San Francisco, 1926. Licensed in California in 1926. Dr Moyle was a member of the Merced-Mariposa Medical Society.

❦

NEEDELS, GEORGE K., Santa Barbara. Died October 1, 1982. Graduate of University of California, Irvine, 1962. Dr Needels was a member of the Santa Barbara County Medical Society.

❦

NELSON, WALDO, Modesto. Died May 14, 1986, aged 70. Graduate of Loma Linda College of Medical Evangelists, 1941. Licensed in California in 1941. Dr Nelson was a member of the Stanislaus Medical Society.

❦

OLRICH, FRANK M., Auburn. Died July 3, 1986, aged 75. Graduate of Rochester School of Medicine, Rochester, New York, 1938. Licensed in California in 1942. Dr Olrich was a member of the Placer-Nevada County Medical Society.

❦

PASTOR, AVRUM E., Burlingame. Died July 7, 1986, aged 55. Graduate of the University of Cincinnati College of Medicine, 1961. Licensed in California in 1962. Dr Pastor was a member of the San Mateo County Medical Society.

❦

PERKINS, EVAN K., Sacramento. Died April 13, 1986, aged 64. Graduate of University of California, San Francisco, 1945. Licensed in California in 1946. Dr Perkins was a member of the Sacramento-El Dorado Medical Society.

❦

PINELES, DEBORAH, Visalia. Died June 6, 1986, aged 76. Graduate of Medical College of Virginia, Richmond, 1939. Licensed in California in 1943. Dr Pineles was a member of the Tulare County Medical Society.

❦

ROSSITTO, THOMAS J., Auburn. Died June 15, 1986, aged 65. Graduate of Creighton School of Medicine, Omaha, 1946. Licensed in California in 1949. Dr Rossitto was a member of the Placer-Nevada County Medical Society.

RUTZ, SAMUEL R., Eureka. Died July 4, 1986, aged 62. Graduate of Northwestern University Medical School, Chicago, 1943. Licensed in California in 1951. Dr Rutz was a member of the Humboldt-Del Norte Medical Society.

❦

SCHEER, ANTON, Belvedere. Died January 24, 1986, aged 83. Licensed in California in 1949. Dr Scheer was a member of the San Francisco Medical Society.

❦

SIEGEL, JOHN M., Newport Beach. Died December 10, 1985, aged 72. Graduate of Jefferson University, Philadelphia, 1938. Licensed in California in 1947. Dr Siegel was a member of the Orange County Medical Association.

❦

SMALE, MILTON L., Bakersfield. Died May 9, 1986, aged 54. Graduate of University of Southern California School of Medicine, 1961. Licensed in California in 1962. Dr Smale was a member of the Kern County Medical Society.

❦

UYENO, YUKIO, Sacramento. Died April 12, 1986, aged 60. Graduate of St Louis University School of Medicine, St Louis, 1955. Licensed in California in 1956. Dr Uyeno was a member of the Sacramento-El Dorado Medical Society.

❦

WARSHAW, BARRY I. Died November 27, 1985, aged 49. Graduate of University of Chicago, 1963. Licensed in California in 1969. Dr Warshaw was a member of the Los Angeles County Medical Association.

❦

WENTZ, ARTHUR EDWARDS, Montecito. Died July 10, 1986, aged 75. Graduate of Ohio State University College of Medicine, Columbus, 1935. Dr Wentz was a member of the Santa Barbara County Medical Society.

❦

WHITWORTH, GEORGE F. IV, Fresno. Died May 22, 1986, aged 60. Graduate of Stanford University School of Medicine, 1949. Licensed in California in 1950. Dr Whitworth was a member of the Fresno-Madera Medical Society.

❦

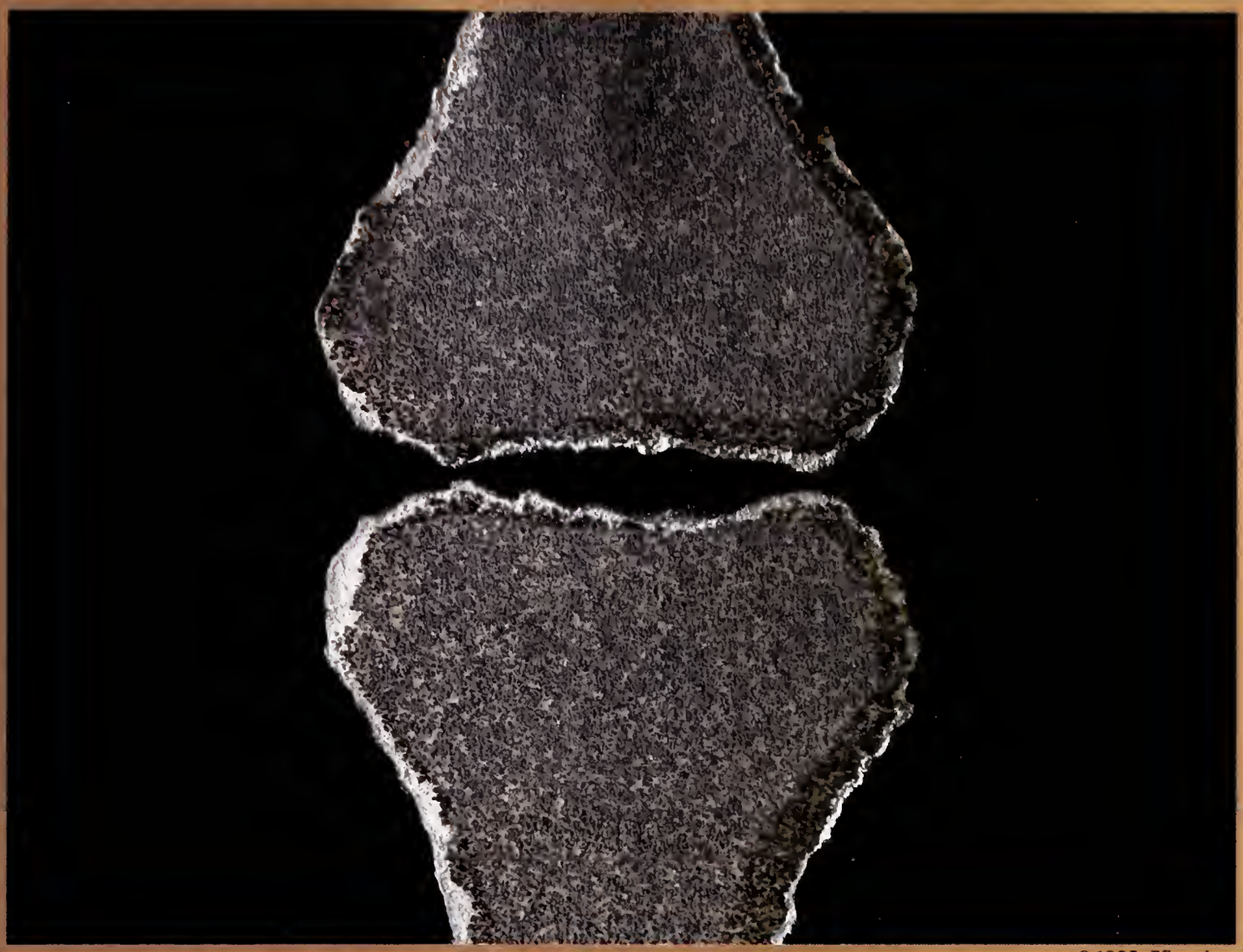
WONDERLY, EARL W., Dinuba. Died May 13, 1986, aged 68. Graduate of Loma Linda College of Medical Evangelists, 1943. Licensed in California in 1943. Dr Wonderly was a member of the Tulare County Medical Society.

❦

YAMSHON, LEONARD J., Los Angeles. Died January 3, 1986, aged 70. Graduate of University of Virginia, 1942. Licensed in California in 1947. Dr Yamshon was a member of the Los Angeles County Medical Association.

Montana Medical Association

DION, ROBERT H., Lewistown. Died August 14, 1986, aged 67. Graduate of Johns Hopkins University, Baltimore, Md, 1943. Dr Dion was a member of the Fergus County Medical Society.



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- it's efficient—once daily, 20-mg dose provides round-the-clock relief,[2] improves compliance and remains effective during long-term therapy.

Feldene® *(PIROXICAM)* *20 mg capsules*

ONE-A-DAY

Please see FELDENE (piroxicam) brief summary on the following page.

Start one-a-day Feldene® (PIROXICAM) 20 mg capsules

For full anti-arthritic action

Prescribe one 20mg capsule daily for convenience and compliance

Source: PDR, 1986, Manufacturers' Prescribing Information.

Indicates maximum dosage for osteoarthritis and rheumatoid arthritis for the antiarthritic agents shown. Consult manufacturers' prescribing information.

Brief Summary

FELDENE® (piroxicam) Capsules

CONTRAINDICATIONS: FELDENE (piroxicam) should not be used in patients who have previously exhibited hypersensitivity to it, or in individuals with the syndrome comprised of bronchospasm, nasal polyps and angioedema precipitated by aspirin or other nonsteroidal anti-inflammatory drugs.

WARNINGS: Peptic ulceration, perforation and G.I. bleeding—sometimes severe, and, in some instances fatal—have been reported with patients receiving FELDENE. If FELDENE must be given to patients with a history of upper gastrointestinal tract disease, the patient should be under close supervision (see ADVERSE REACTIONS)

PRECAUTIONS: Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of piroxicam to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally, nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of an NSAID may cause a dose-dependenf reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly.

Because of extensive renal excretion of piroxicam and its biotransformation products (less than 5% of the daily dose excreted unchanged), lower doses of piroxicam should be anticipated in patients with impaired renal function, and they should be carefully monitored.

Although other nonsteroidal anti-inflammatory drugs do not have the same direct effect on platelets that aspirin does, all drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree.

Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop visual complainfs during treatment with FELDENE have ophthalmic evaluation.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom abnormal liver tests have occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with FELDENE.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis have been reported with FELDENE. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), FELDENE should be discontinued. (See also ADVERSE REACTIONS.)

Although at the recommended dose of 20 mg/day of FELDENE increased fecal blood loss due to gastrointestinal irritation did not occur, in about 4% of the patients treated with FELDENE alone or concomitantly with aspirin, reductions in hemoglobin and hematocrit values were observed.

Peripheral edema has been observed in approximately 2% of the patients treated with FELDENE. Therefore, FELDENE should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

A combination of dermatological and/or allergic signs and symptoms suggestive of serum sickness have occasionally occurred in conjunction with the use of FELDENE. These include arthralgias, pruritus, fever, fatigue, and rash including vesiculo bullous reactions and exfoliative dermatitis.

DRUG INTERACTIONS: Interactions with coumarin-type anticoagulants have been reported with FELDENE since marketing. Therefore, physicians should closely monitor patients for a change in dosage requirements when administering FELDENE to patients on coumarin-type anticoagulants and other highly protein-bound drugs.

Plasma levels of piroxicam are depressed to approximately 80% of their normal values when FELDENE is administered in conjunction with aspirin (3900 mg/day), but concomitant administration of antacids has no effect on piroxicam plasma levels.

Nonsteroidal anti-inflammatory agents, including FELDENE, have been reported to increase steady state plasma lithium levels. It is recommended that plasma lithium levels be monitored when initiating, adjusting and discontinuing FELDENE.

Carcinogenesis, Chronic Animal Toxicity and Impairment of Fertility: Subacute and chronic toxicity studies have been carried out in rats, mice, dogs, and monkeys.

The pathology most often seen was that characteristically associated with the animal toxicology of anti-inflammatory agents: renal papillary necrosis (see PRECAUTIONS) and gastrointestinal lesions.

In classical studies in laboratory animals, piroxicam did not show any teratogenic potential.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy and Nursing Mothers: Like other drugs which inhibit the synthesis and release of prostaglandins, piroxicam administration continued late into pregnancy increased the incidence of dystocia and delayed parturition in animals. Gastrointestinal tract toxicity was increased in pregnant females in the last trimester of pregnancy compared to non-pregnant females or females in earlier trimesters of pregnancy.

FELDENE is not recommended for use in nursing mothers or in pregnant women because of the animal findings and since safety for such use has not been established in humans.

Use in Children: Dosage recommendations and indications for use in children have not been established

ADVERSE REACTIONS: Gastrointestinal symptoms are the most prominent side effects, occurring in approximately 20% of the patients, which in most instances did not interfere with the course of therapy. Of the patients experiencing gastrointestinal side effects, approximately 5% discontinued therapy with an overall incidence of peptic ulceration of about 1%.

Adverse reactions are listed below by body system for all patients in clinical trials with FELDENE (piroxicam) at doses of 20 mg/day

Incidence Greater Than 1%: The following adverse reactions occurred more frequently than 1 in 100.

Gastrointestinal: stomatitis, anorexia, epigastric distress,* nausea,* constipation, abdominal discomfort, flatulence, diarrhea, abdominal pain, indigestion

Hematological: decreases in hemoglobin* and hematocrit* (see PRECAUTIONS), anemia, leucopenia, eosinophilia

Dermatologic: pruritus, rash

Central Nervous System: dizziness, somnolence, vertigo

Urogenital: BUN and creatinine elevations (see PRECAUTIONS)

Body as a Whole: headache, malaise

Special Senses: tinnitus

Cardiovascular/Respiratory: edema (see PRECAUTIONS)

* Reactions occurring in 3% to 9% of patients treated with FELDENE

Reactions occurring in 1% to 3% of patients are unmarked

Incidence Less Than 1% (Causal Relationship Probable): The following adverse reactions occurred less frequently than 1 in 100. The probability exists that there is a causal relationship between FELDENE and these reactions

Gastrointestinal: liver function abnormalities, jaundice, hepatitis (see PRECAUTIONS), vomiting, hematemesis, melena, gastrointestinal bleeding, perforation and ulceration (see WARNINGS), dry mouth

Hematological: thrombocytopenia, petechial rash, ecchymosis, bone marrow depression including aplastic anemia, epistaxis

Dermatologic: sweating, erythema, bruising, desquamation, exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, vesiculo bullous reactions, photoallergic skin reactions

Central Nervous System: depression, insomnia, nervousness

Urogenital: hematuria, proteinuria, interstitial nephritis, renal failure, hyperkalemia, glomerulitis, papillary necrosis, nephrotic syndrome (see PRECAUTIONS)

Body as a Whole: pain (colic), fever, flu-like syndrome (see PRECAUTIONS)

Special Senses: swollen eyes, blurred vision, eye irritations

Cardiovascular/Respiratory: hypertension, worsening of congestive heart failure (see PRECAUTIONS), exacerbation of angina

Metabolic: hypoglycemia, hyperglycemia, weight increase, weight decrease

Hypersensitivity: anaphylaxis, bronchospasm, urticaria/angioedema, vasculitis, "serum sickness" (see PRECAUTIONS)

Incidence Less Than 1% (Causal Relationship Unknown): Other adverse reactions were reported with a frequency of less than 1 in 100, but a causal relationship between FELDENE and the reaction could not be determined

Gastrointestinal: pancreatitis

Dermatologic: onycholysis, loss of hair

Central Nervous System: akathisia, hallucinations, mood alterations, dream abnormalities, mental confusion, paresthesias

Urogenital System: dysuria

Body as a Whole: weakness

Cardiovascular/Respiratory: palpitations, dyspnea

Hypersensitivity: positive ANA

OVERDOSAGE: In the event treatment for overdosage is required, the long plasma half-life of piroxicam should be considered. The absence of experience with acute overdosage precludes characterization of sequelae and recommendations of specific antidotal efficacy at this time. It is reasonable to assume that the standard measures of gastric evacuation and general supportive therapy would apply. In addition to supportive measures, the use of activated charcoal may effectively reduce the absorption and reabsorption of piroxicam. Experiments in dogs have demonstrated that the use of multiple-dose treatments with activated charcoal could reduce the half-life of piroxicam elimination from 27 hours (without charcoal) to 11 hours and reduce the systemic bioavailability of piroxicam by as much as 37% when activated charcoal is given as late as 6 hours after administration of piroxicam.

ADMINISTRATION AND DOSAGE: Rheumatoid Arthritis, Osteoarthritis: It is recommended that FELDENE therapy be initiated and maintained at a single daily dose of 20 mg. If desired, the daily dose may be divided.

Dosage recommendations and indications for use in children have not been established.

More detailed professional information available on request.

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References: 1. Siegmeth W: Serum concentrations of piroxicam in relation to its clinical effect in patients with chronic polyarthritis (trans). *Wien Med Wochenschr* 130:31-35, 1980. 2. Tausch: Placebo-controlled study of piroxicam in the treatment of rheumatoid arthritis. *Am J Med* (report) 72:18-22, February 16, 1982.

Pfizer **LABORATORIES DIVISION**
PFIZER INC

(Continued from Page 466)

February 8-13—**General Internal Medicine: Concepts and Controversies.** UCSF at Hyatt Lake Tahoe, Nevada. Sunday-Friday. Contact: UCSF

February 12-14—**20th Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. 15 hrs. Contact: UCSF.

March 11—**Rheumatology: Osteoarthritis and Nonsteroidal Drugs.** LLU. Wednesday. 9 hrs. Fee: $60. Contact: LLU.

March 30-April 1—**Federation of Western Societies of Neurological Science 24th Annual Meeting.** Monday-Wednesday at Hotel Del Coronado, Coronado. Contact: Patrick D. Lyden, MD, Dept of Neurosciences, UCSD Medical Center H-815A, 225 W Dickinson St, San Diego 92103. (619) 452-3940.

OB/GYN

October 20-24—**16th Annual Review Course in Obstetrics and Gynecology.** USC at Pasadena Hilton Hotel. Monday-Friday. 38 hrs. Fee: $545. Contact: USC.

October 20-24—**Comprehensive Review Course and Annual Postgraduate Course.** UCSF at San Francisco Hilton Hotel. Monday-Friday. 32 hrs. Fee: $525. Contact: UCSF.

October 20-25—**9th Annual Review Course in Clinical Obstetrics and Gynecology and/or Gynecological Histopathology.** UCI at Westin South Coast Plaza, Costa Mesa. Monday-Saturday. 17-46.5 hrs. Contact: UCI.

October 25—**Review Course for Gynecologic Pathology.** USC at Pasadena Hilton Hotel. Saturday. 6 hrs. Fee: $105. Contact: USC.

November 1-2—**Changing Trends in Gynecologic Practice.** UCI at Rancho Mirage. Saturday-Sunday. 10 hrs. Contact: UCI.

November 7—**Advances in the Management of Gynecological Cancer.** Sutter Community Hospitals at Sacramento Inn. Friday. 6 hrs. Fee: $70. Contact: Peggy Coit, Sutter Shared Services, 2020 "I" St, Ste D, Sacramento 95814. (916) 446-7684.

December 4-6—**33rd Annual Scientific Meeting—Nebraska OB/GYN Society.** University of Nebraska at MGM Grand Hotel, Las Vegas, Nevada. Thursday-Saturday. 9 hrs. Fee: $200. Contact: Dennis Beavers, MD, 720 N 87th St, Omaha, NE 68114. (402) 390-1200.

December 4-7—**Current Issues in Perinatal Medicine.** UCI at Desert Princess Hotel, Palm Springs. Thursday-Sunday. Contact: UCI.

December 10—**Lifestyles and Perinatal Outcome.** Perinatal Advisory Council of Los Angeles Communities at Broadway Plaza Hyatt Regency, Los Angeles. Wednesday. 7 hrs. Fee: $75. Contact: Marilyn Cejka Steinberg, PAC, 3250 Wilshire Blvd, Ste 206, Los Angeles 90010. (213) 380-1790.

December 11-13—**Advanced Ultrasound.** American College of OB/GYN at Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. 16 hrs. Contact: ACOG, 600 Maryland Ave SW, Ste 300 East, Washington, DC 20024-2588. (202) 863-2542.

January 16-18—**Gynecology Update for the Primary Care Physician.** UCSD at Vacation Village Resort, San Diego. Friday-Sunday. 15 hrs. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

February 8-12—**15th Obstetric Anesthesia Conference.** Ohio State University Hospital at Sheraton Waikiki Hotel, Hawaii. Sunday-Thursday. Contact: OSU Hospital, Dept of Anesthesiology, 410 W 10th Ave, Columbus, OH 43210. (614) 421-8487.

February 21—**Infertility Update IV.** Scripps Clinic and Research Foundation, La Jolla. Saturday. 6 hrs. Contact: Bonny Mower, Dept of Academic Affairs, Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

March 25-28—**GYN Urology.** UCI at Hilton Riviera, Palm Springs. Wednesday-Saturday. Contact: UCI.

OPHTHALMOLOGY

December 11-12—**An Update in Neuro-Ophthalmology.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Friday. Contact: UCSF.

February 1-5—**6th Annual Squaw Valley Retinal Symposium.** UCD at Tahoe City. Sunday-Thursday. Fee: $360. Contact: J. Robert Griffin, MD, 107 Scripps Dr, Ste 110, Sacramento 95825. (916) 929-2525.

PATHOLOGY

October 20-25—**9th Annual Review Course in Clinical Obstetrics and Gynecology and/or Gynecological Histopathology.** UCI at Westin South Coast Plaza, Costa Mesa. Monday-Saturday. Contact: UCI.

October 25—**Review Course for Gynecologic Pathology.** USC at Pasadena Hilton Hotel. Saturday. 6 hrs. Fee: $105. Contact: USC.

PEDIATRICS

October 16-18—**Practical Topics in Pediatric Nutrition.** UCSF. Thursday-Saturday. 13 hrs. Fee: $300. Contact: UCSF.

October 24-25—**Pediatric Symposium.** Kaiser Permanente Medical Group at Biltmore Hotel, Los Angeles. Friday-Saturday. 12 hrs. Fee: $150. Contact: Judy Harrison, Dept of Clinical Services, Southern California Permanente Medical Group, 393 E Walnut St, Pasadena 91188. (818) 405-5000.

October 25-November 1—**Pediatrics for the Practitioner.** UCI at Mauna Kea Hotel, Hawaii. One week. 20 hrs. Contact: UCI.

October 31-November 1—**Paroxysmal Disorders of Childhood.** UCSF at Mark Hopkins Hotel, San Francisco. Friday-Saturday. 7 hrs. Fee: $150. Contact: UCSF.

November 13-15—**New Approaches in Children's Orthopaedics.** UCD at Monterey Plaza, Monterey. Thursday-Saturday. 9 hrs. Fee: $340. Contact: UCD.

November 21-24—**8th Annual American Academy of Pediatrics Las Vegas Seminars: Pediatric Update.** American Academy of Pediatrics at Caesars Palace, Las Vegas. Friday-Monday. 15.5 hrs. Fee: $295. Contact: AAP, PO Box 2134, Inglewood 90305. (213) 757-1198.

December 6—**5th Annual Binational Workshop: Border Health Problems—Pediatrics Infectious Disease.** Children's Hospital, San Diego. Saturday. 5 hrs. Contact: Ann Albrecht, Children's Hospital, 8001 Frost St, San Deigo 92123. (619) 576-1700

January 19-21—**Pediatrics for the Primary Care Physician.** UCSD at Vacation Village Resort, San Diego. Monday-Wednesday. 16 hrs. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 24-31—**Pediatric Emergencies.** Scripps Memorial Hospital, Encinitas at Kona Surf Resort, Hawaii. One week. 21 hrs. Fee: $375. Contact: Edith Bookstein/AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

January 30-February 1—**25th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Marriott Hotel. Friday-Sunday. 15 hrs. Fee: $175. Contact: Wayne Herbert, MD, Children's Hospital of Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

February 3-8—**16th Annual Pediatric Postgraduate Course: Pediatric Update 1987.** Schneider Children's Hospital of Long Island Jewish Medical Center, Rancho Las Palmas, Palm Springs. Tuesday-Sunday. Contact: Ann J. Boehme, Schneider Children's Hospital of Long Island Jewish Medical Center, New Hyde Park, NY 11042. (718) 470-8650.

February 5-7—**Current Concepts in Pediatric Medicine.** American Academy of Pediatrics at Holiday Inn Embarcadero, San Diego. Thursday-Saturday. 16 hrs. Fee: $330. Contact: Neal A. Baker, AAP, Division of Continuing Education, PO Box 927, Elk Grove Village, IL 60007. (800) 433-9016, or in Illinois (800) 421-0589.

February 16-18—**Pediatrics Update 1987.** Continuing Medical Education Associates at Hyatt Islandia Hotel, San Diego. Monday-Wednesday. 18 hrs. Fee: $275. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

March 5-7—**Advances in Pediatrics II.** American Academy of Pediatrics at Kauai, Hawaii. Thursday-Saturday. 16 hrs. Fee: $330. Contact: Neal A. Baker, Div of Continuing Education, AAP, PO Box 927, Elk Grove Village, IL 60007. (800) 433-9016, or in Illinois (800) 421-0589.

PSYCHIATRY

October 24-26—**1986 Self-Psychology Conference: Clinical Advances in Self-Psychology.** UCSD at Vacation Village Resort, San Diego. Friday-Sunday. 16.5 hrs. Fee: $275. Contact: UCSD.

December 28-January 3—**Psychiatry and the Practicing Physician—"New Year '87—Maui."** Hawaii Medical Association at Royal Lahaina Resort, Kaanapali Beach, Maui. Sunday-Saturday. 16.5 hrs. Fee: $385. Contact: Joe Harrison, MD, Symposium Maui, Inc, PO Box 10185, Lahaina, HI 96761. (808) 879-8182.

January 25-30—**13th Annual Midwinter Program for Psychiatrists: Special Focus on Adolescent Psychiatry.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sunday-Friday. 25 hrs. Fee: $355-415. Contact: UCD.

RADIOLOGY

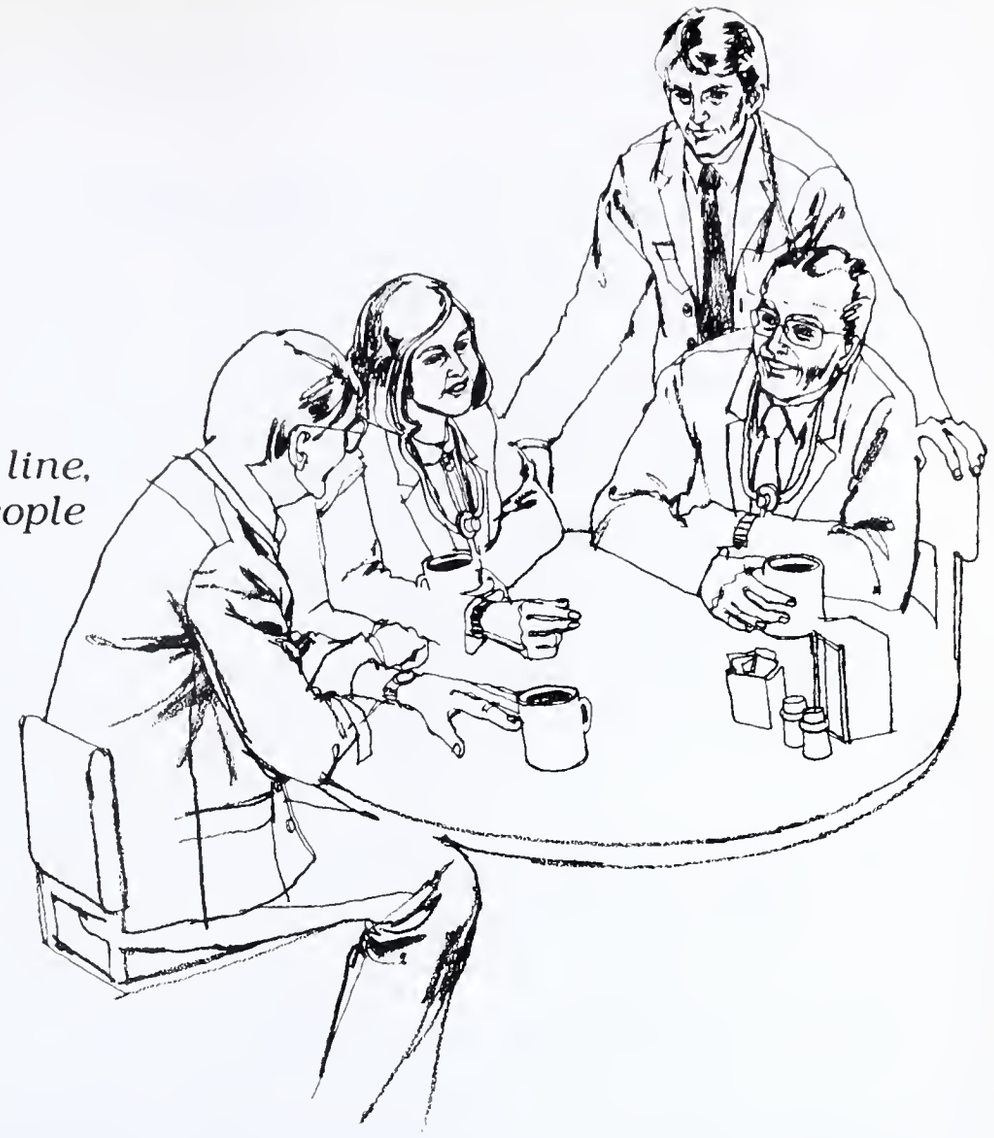
October 25-29—**Radiology.** USC at Kauai, Hawaii. Saturday-Wednesday. 27 hrs. Fee: $535. Contact: USC.

October 30-November 1—**San Diego Imaging Symposium.** UCSD at US Grant Hotel, San Diego. Thursday-Saturday. 14 hrs. Contact: R. Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

November 3-7—**Diagnostic Radiology Seminars.** UCSF at Maui Marriott Hotel, Hawaii. Monday-Friday. Contact: UCSF.

November 15-16—**Magnetic Resonance Imaging.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Saturday-Sunday. 10 hrs. Fee: $200. Contact: LARS-MRI, PO Box 91215, Los Angeles 90009-1215. (213) 642-0921.

(Continued on Page 566)



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(Continued from Page 564)

December 11-13—**Advanced Ultrasound.** American College of OB/GYN at Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. 16 hrs. Contact: ACOG, 600 Maryland Ave SW, Ste 300 East, Washington, DC 20024-2588. (202) 863-2542.

January 9-12—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz Carlton Hotel, Laguna Niguel. Friday-Monday. Contact: UCSD.

January 9-13—**Advance Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Hotel, Laguna Niguel. Friday-Tuesday. 20 hrs. Contact: Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 13-16—**Chest Radiology—1987.** UCSD at Hotel Del Coronado, Coronado. Tuesday-Friday. 22 hrs. Contact: Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 16-18—**Annual Update on Nuclear Radiology.** UCSD at Hotel Del Coronado, San Diego. Friday-Sunday. Fee: $400. Contact: R. Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 22-24—**Practical Approach to Duplex Imaging.** UCSD at San Diego Hilton Hotel. Thursday-Saturday. Contact: UCSD.

January 30-February 1—**39th Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. 21 hrs. Fee: $350. Contact: Diane L. Johnson, Los Angeles Radiological Society, 5200 Century Blvd, Ste 920, Los Angeles 90045. (213) 642-0921.

February 2-6—**Radiology: Imaging and Intervention.** UCSD at Hotel Inter-Continental, San Diego. Monday-Friday. Contact: R. Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

February 3-7—**13th Annual Midwinter Radiological Post Conference Seminar.** Los Angeles Radiological Society at Hyatt Regency, Kaanapali, Maui, Hawaii. Tuesday-Saturday. 18 hrs. Fee: $375. Contact: LARS-MWRC, PO BOX 91215, Los Angeles 90009-1215. (213) 642-0921.

February 11—**Interventional Radiology.** LLU at LLU. Wednesday. 8 hrs. Fee: $60. Contact: LLU.

February 21-28—**Radiology for Emergency and Primary Care Physicians.** Scripps Memorial Hospital, Encinitas at Royal Lahaina Resort, Maui, Hawaii. One week. 21 hrs. Fee: $375. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

March 2-5—**Neuroradiology Update.** UCSD at Hotel Del Coronado, Coronado. Monday-Thursday. Contact: Mary J. Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

March 3-6—**Magnetic Resonance Imaging.** UCSD at Hotel Del Coronado, Coronado. Tuesday-Friday. Contact: Mary J. Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

March 16-21—**Diagnostic Imaging—1987.** UCSF at Waiohai Hotel, Kauai, Hawaii. Monday-Saturday. Contact: UCSF.

SPORTS MEDICINE

November 25-28—**Sports Medicine.** American College of Sports Medicine and Children's Hospital Medical Center, Oakland at Inter-Continental Hotel, Maui. Tuesday-Friday. 25 hrs. Fee: $300. Contact: Stuart Zeman, MD, Course Chairman, 2999 Regent St, Ste 203, Berkeley 94705. (415) 540-8686.

December 10—**Orthopedic Surgery: Sports Injuries.** LLU at LLU. Wednesday. 6 hrs. Fee: $60. Contact: LLU.

SURGERY

October 18-19—**1986 Regional Review Course in Hand Surgery.** American Society for Surgery of the Hand at Orthopaedic Hospital, Los Angeles. Saturday-Sunday. 12 hrs. Fee: $200. Contact: American Society for Surgery of the Hand, 3025 S Parker Rd, Ste 65, Aurora, CO 80014. (303) 755-4588.

October 18-25—**8th International Seminar on Operative Arthroscopy.** UCLA at Maui, Hawaii. One week. Contact: UCLA.

October 18-25—**Temporal Bone Surgical Dissection and Cochlear Implant.** House Ear Institute, Los Angeles. One week. 62 hrs. Fee: $900. Contact: Antonio De La Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

October 24-26—**The Practical Applications of Recent Advances in Neurosurgery Research.** Scripps Clinic and Research Foundation, La Jolla. Friday-Sunday. 16.5 hrs. Fee: $250. Contact: Dept of Academic Affairs, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

November 1-8—**Temporal Bone Surgical Dissection and Cochlear Implant Courses.** House Ear Institute. One week. 62 hrs. Fee: $900. Contact: Antonio De La Cruz, MD, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

November 10-14—**Cochlear Implant.** House Ear Institute. Monday-Friday. 32 hrs. Fee: $1,350. Con-

THE KUZELL INSTITUTE SYMPOSIA

St. Francis Hotel, San Francisco, California

FRIDAY, NOVEMBER 14

Arthritis: Pathogenesis and Treatment

Inflammation, Robert O. Webster, PhD

Rheumatoid Arthritis, Nathan J. Zvaifler, MD

Remission-Inducing Drugs, Robert F. Willkins, MD

Biotechnology, C. Garrison Fathman, MD

Infectious Agents in Arthritis, Frank R. Schmid, MD

Spondyloarthritis, Andrei Calin, MD

Ocular Inflammation, James T. Rosenbaum, MD

Lyme Disease, Allen Steere, MD

SATURDAY, NOVEMBER 15

Therapeutic Advances in Infectious Diseases

New Antibiotics, Harold C. Neu, MD

The Promise of the Quinolones, Donald Kaye, MD

Infection in the Cancer Patient, Jean Klastersky, MD

Controversies About Prophylaxis and Treatment, Gerald P. Bodey, MD

Anerobic Infections, Sherwood Gorbach, MD

AIDS Symposium, Michael Gottlieb, MD, Paul Volberding, MD, Jack S. Remington, MD, Lowell S. Young, MD

ADMISSION:
No Fee for Attendance

REGISTRATION AND ACCREDITATION FEE:
$15.00/day (Fee includes Category I Credit and Lunch) 6.5 hours Category I—November 14 7.5 hours Category I—November 15

FOR FURTHER INFORMATION:
Division of Education, Pacific Presbyterian Medical Center, P.O. Box 7999, San Francisco, CA 94120, (415) 923-3440

Kuzell Institute for Arthritis and Infectious Diseases
Pacific Presbyterian Medical Center
For Northern California doctors only

CONTINUING MEDICAL EDUCATION

tact: Antonio De La Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

December 4-7—**2nd Annual Fracture Management Symposium.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Thursday-Sunday. 18 hrs. Fee: $475. Contact: UCD.

December 7-19—**Temporal Bone Surgical Dissection and Cochlear Implant.** House Ear Institute. Sunday-Friday. 100 hrs. Fee: $1,700. Contact: Antonio De La Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

January 19-21—**American Society for Surgery of the Hand's 1st Winter Meeting.** Pacific Medical Center, San Francisco. Monday-Wednesday. Contact: American Society for Surgery of the Hand, 3025 S Parker Rd, Ste 65, Aurora, CO 80014.

January 19-23—**10th Annual Postgraduate Assembly in Surgery.** UCSD at US Grant Hotel, San Diego. Monday-Friday. 26.5 hrs. Contact: UCSD.

March 6-8—**Cruciate Ligament Surgery: Principles and Practice.** Scripps Clinic and Research Foundation at Marriott Hotel, La Jolla. Friday-Sunday. 23 hrs. Contact: Bonny A. Mower, Dept of Academic Affairs, Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

March 30-April 10—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Monday-Friday. 100 hrs. Fee: $1,750. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

OF INTEREST TO ALL PHYSICIANS

October 16-19—**Clinical Biofeedback Certificate Program.** UCLA. Thursday-Sunday. 24 hrs. Fee: $195. Contact: UCLA.

October 17-19—**Practical Gastroenterology and Flexible Sigmoidoscopy for the Practicing Physician.** UCSD and Continuing Medical Education Associates at Vacation Village Resort, San Diego. Friday-Sunday. 20 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

October 19-21—**Alcohol Related Birth Defects.** UCSD at Kona Kai Resort, San Diego. Sunday-Tuesday. 13.5 hrs. Contact: UCSD.

October 22—**Update on Diabetes.** Hospital of Good Samaritan, Los Angeles at Moseley-Salvatori Conference Center, Los Angeles. Wednesday. 7 hrs. Contact: Dolores Gay, 616 S Witmer St, Los Angeles 90017. (213) 977-2352.

October 23-25—**International Conference.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. Contact: UCSF.

October 23-25—**Postgraduate Institute for Monterey Counties.** CMA at Sheraton, Monterey. Thursday-Saturday. Contact: Janice Rigney, CMA.

October 31—**Managing and Controlling Asbestos Contamination/Exposure.** USC. Friday. Fee: $150. Contact: USC.

October 31-November 2—**30th Annual Western Occupational Health Conference.** Western Occupational Medical Association at Golden Gateway Holiday Inn, San Francisco. Friday-Sunday. 14 hrs. Fee: $175. Contact: Joe Donovan, WOMA, 433 Palmer Ave, Aptos 95003. (408) 688-9667.

November 3-6—**Intervention Workshop.** Scripps Memorial Hospital. Monday-Thursday. 26.5 hrs. Fee: $250. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

November 5—**Common Musculo-Skeletal Problems.** Veterans Administration Medical Center, Sepulveda. Wednesday. 5 hrs. Contact: Arun J. Mehta, MD, Rehabilitation Medicine Service (117), VAMC, Sepulveda 91343. (818) 891-2473.

November 7-8—**Medical Advances in the 80s: A Multi-Specialty Update—UCD 20th Anniversary.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. Contact: UCD.

November 8-10—**State of the Art Urology—Live Television Coverage of Surgery.** UCLA at Miramar Sheraton Hotel, Santa Monica. Saturday-Monday. 21 hrs. Fee: $400. Contact: UCLA.

November 10-13—**Primary Care Update: 71st Scientific Assembly of Interstate Postgraudate Medical Association of North America.** Town and Country Hotel, San Diego. Monday-Thursday. 24 hrs. Contact: IPMANA, PO Box 1109, Madison, WI 53701. (608) 257-6781.

November 10-14—**Intensive Care.** STAN at STAN. Monday-Friday. Contact: STAN.

November 13-15—**Progress in Impotence: Diagnosis and Therapy.** UCSD at US Grant Hotel, San Diego. Thursday-Saturday. 13 hrs. Fee: $295. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

November 14—**22nd Annual California Medical Center Staff Seminar: New Concepts in Medicine.** Los Angeles. Friday. 6 hrs. Fee: $50. Contact: California Medical Center, Kenneth L. Senter, MD, 1414 S Hope St, Los Angeles 90015. (213) 742-5750.

November 14-16—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital and Continuing Medical Education Associates at Hotel Del Coronado, San Diego. Friday-Sunday. 18 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

November 21—**Orthopedic Symposium.** Kaiser Permanente Medical Group at Marina Beach Hotel, Marina Del Rey. Friday. 7 hrs. Fee: $100. Contact: Judy Harrison, Dept of Clinical Services, Southern California Permanente Medical Group, 393 E Walnut St, Pasadena 91188. (818) 405-5000.

November 22—**Alzheimer's Disease—An Overview.** UCI at UCI. Saturday. 5.5 hrs. Contact: UCI.

November 29-December 6—**Behavioral Medicine Topics That Make Sense for Your Practice—Hawaiian Island Cruise Adventure.** University of Arizona at Hawaii. One week. 24 hrs. Contact: Epic Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

December 5-6—**2nd Annual Clinical Nutrition Update for the Practicing Physician.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 12 hrs. Fee: $165. Contact: UCD.

December 5-6—**Psychosocial Intervention in Cancer and AIDS.** University of Illinois College of Medicine at La Jolla Marriott Hotel, La Jolla. Friday-Saturday. 13 hrs. Fee: $150. Contact: Carle Medical Communications, 510 West Main, Urbana, IL 61801. (217) 384-4838.

December 5-7—**3rd Annual Common Office Problems for the Primary Care Physician.** Cypress Foundation at Hyatt Regency, Monterey. Friday-Sunday. 12 hrs. Contact: Cypress Foundation, PO Box 80308, Salinas 93912. (408) 455-1833.

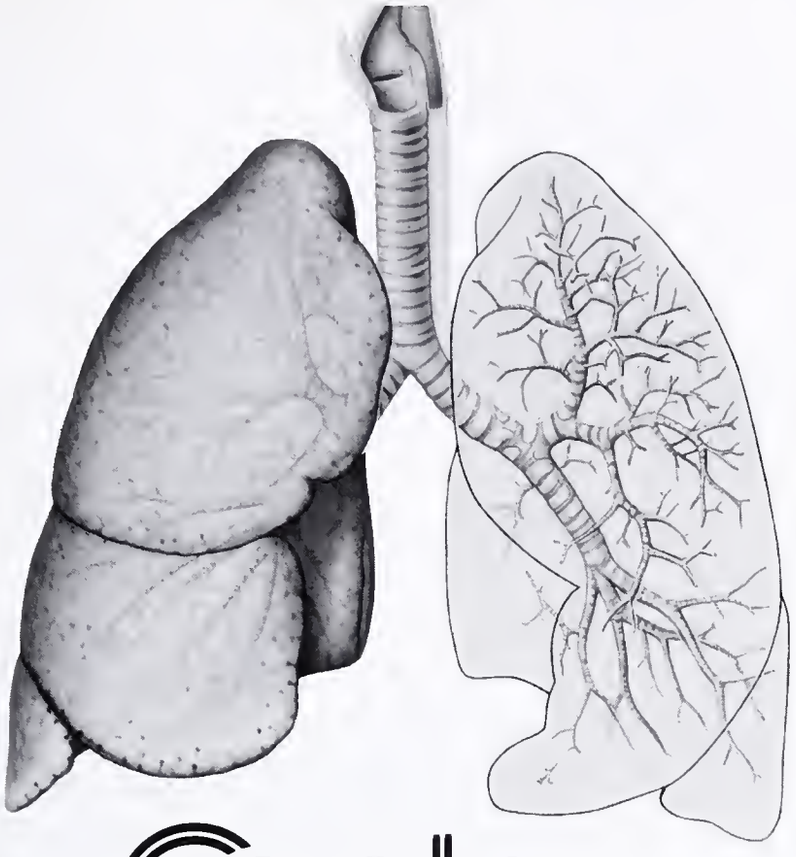
December 9—**Acquired Immune Deficiency Syndrome: Update 1986.** Daniel Freeman Memorial Hospital, Inglewood. Tuesday. 6 hrs. Contact: Daniel Freeman Memorial Hospital, (213) 674-7050, ext 3427.

December 11-12—**AIDS and the Nervous System.** UCSF at St Francis Hotel, San Francisco. Thursday-Friday. 11 hrs. Contact: UCSF.

January 12-16—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD at San Diego Hilton Hotel. Monday-Friday. 32 hrs. Fee: $325-400. Contact: UCSD.

(Continued on Page 570)

Consider the causative organisms...



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Haemophilus influenzae, H influenzae, Streptococcus pneumoniae, Streptococcus pyogenes
(ampicillin-susceptible) (ampicillin-resistant)

Note: Ceclor® is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

Ceclor® (cefaclor)

Summary. Consult the package literature for prescribing information.

Indications: Lower respiratory infections, including pneumonia, caused by susceptible strains of *Streptococcus pneumoniae, Haemophilus influenzae,* and *S. pyogenes* (group A beta-hemolytic streptococci).

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Warnings: CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:

- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- In renal impairment, safe dosage of Ceclor may be lower than that usually recommended. Ceclor should be administered with caution in such patients.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include:

- Gastrointestinal (mostly diarrhea): 2.5%.
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, erythema multiforme, serum-sickness-like reactions): 1.5%; usually subside within a few days after cessation of therapy. These reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.
- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1%.

Abnormalities in laboratory results of uncertain etiology

- Slight elevations in hepatic enzymes.
- Transient fluctuations in leukocyte count (especially in infants and children)
- Abnormal urinalysis; elevations in BUN or serum creatinine
- Positive direct Coombs' test
- False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (glucose enzymatic test strip, Lilly)

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Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285.

Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630

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(Continued from Page 568)

January 16-17—**Cardiology for the Non-Cardiologist.** UCI at Long Beach. Friday-Saturday. Contact: UCI.

January 18-20—**Physical Examination of the Child Sexual Molest Victim: The State of the Art.** Children's Hospital, San Diego at Hanalei Hotel, San Diego. Sunday-Tuesday. 15.5 hrs. Fee: $200. Contact: Ann Albrecht, Children's Hospital, 8001 Frost St, San Diego 92123. (619) 576-1700.

January 18-23—**Nevada Academy of Family Physicians Winter Assembly: Living Healthier Longer.** Caesar's Tahoe Hotel and Casino, Nevada. Sunday-Friday. 34 hrs. Fee: $400. Contact: Dottie Batchelor, NAFP, PO Box 7471, Reno, NV 89510-7471. (702) 826-5100.

January 19-21—**Pediatrics for the Primary Care Physician.** UCSD at Vacation Village Resort, San Diego. Monday-Wednesday. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 20-24—**Intensive Course in Geriatric Medicine.** UCLA at Santa Monica. Tuesday-Saturday. 33 hrs. Contact: UCLA.

January 23-25—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** Continuing Medical Education Associates at San Diego. Friday-Sunday. 20 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

January 26-28—**Recent Advances in Geriatric Medicine—1987.** UCSD at Holiday Inn Embarcadero, San Diego. Monday-Wednesday. 18 hrs. Contact: UCSD.

January 28-30—**Neurology for Non-Neurologists.** UCSD at Holiday Inn Embarcadero, San Diego. Wednesday-Friday. 21 hrs. Fee: $375. Contact: UCSD.

January 30-February 1—**Primary Care Update—1987: A Practical Approach.** Scripps Clinic and Research Foundation at Vacation Village Resort, San Diego. Friday-Sunday. Fee: $200. Contact: Bonny Mower, Dept of Academic Affairs, PO Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

February 4-6—**4th Annual Practical Advances in Medicine.** Cypress Foundation at Carmel Mission Inn, Carmel. Wednesday-Friday. 16 hrs. Contact: Cypress Foundation, PO Box 80308, Salinas 93912. (408) 455-1833.

February 7-8—**2nd Triennial Diabetes Update.** Cypress Foundation at Hyatt Regency, Monterey. Saturday-Sunday. 10 hrs. Contact: Cypress Foundation, PO Box 80308, Salinas 93912. (408) 455-1833.

February 9-14—**UCI Family Practice Refresher Course.** UCI at Newport Beach. Monday-Saturday. Contact: UCI.

February 13-15—**Office Gynecology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Islandia Hotel, San Diego. Friday-Sunday. 18 hrs. Fee: $275. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

February 21-28—**Radiology for Emergency and Primary Care Physicians.** Scripps Memorial Hospital, Encinitas at Royal Lahaina Resort, Maui, Hawaii. One week. 21 hrs. Fee: $375. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

March 9-13—**Hawaii '87: Critical Issues in Primary Care.** Hawaii Medical Association at Waiohai Hotel, Poipu Beach. Monday-Friday. 20 hrs. Contact: Valerie Murray, Pacfic Institute of Continuing Medical Education, PO Box 1059, Koloa, Kauai, HI 96756. 1 (808) 742-7471.

March 13-15—**Office Emergencies in Primary Care.** Sharp Memorial Hospital at Hotel Del Coronado, Coronado. Friday-Sunday. 18 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

March 19-27—**Specialty Series in Primary Care: Cardiology, Infectious Diseases and Endocrinology.** UCSD at Palm Springs Spa Hotel. Thursday-Friday. Contact: UCSD.

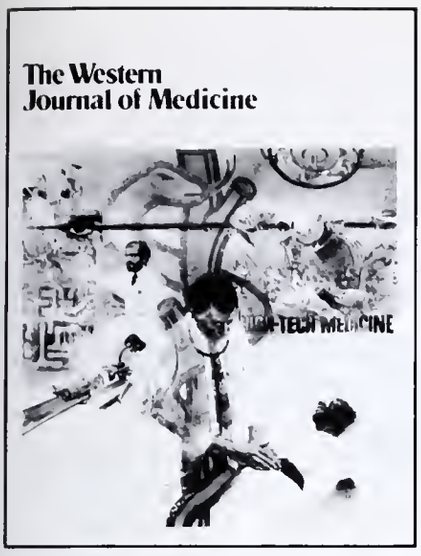
IDAHO

December 27-January 3—**Internal Medicine.** Sun Valley. One week. Sponsor: University of Washington School of Medicine. Contact: U/W School of Medicine, Division of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 14-21—**How to Make Fitness and Health Promotion Work in Your Practice.** Sun Valley. One week. 24 hrs. Sponsors: University of Arizona, Department of Family and Community Medicine, and Epic Medical Expeditions. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley 83353. (208) 788-4995.

(Continued on Page 572)

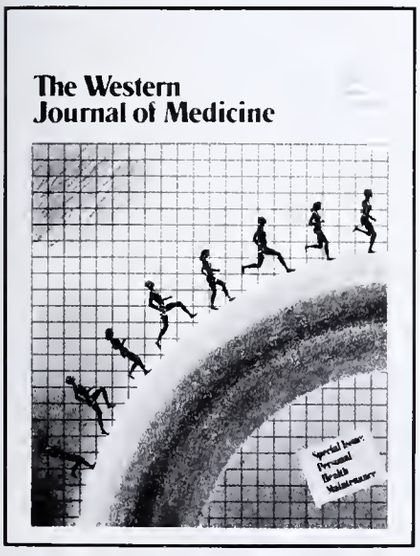
High-Tech Medicine



Progress in medical science seems to come in rushes. There are long periods of time during which we mainly fine-tune the status quo: third-generation drugs, better optics for endoscopes, more accurate assays, rapid development of x-ray film and so forth. Then, out of nowhere, a surge of new discoveries whose potential applications to medical practice seem limitless takes our breath away. We are now in such an epoch. Powerful and precise lasers. Almost unbelievable organ transplantation. Complex and uniquely informative magnetic resonance imaging and positron emission tomography. Exquisitely specific monoclonal antibodies. And the immense potential of modern molecular biology. This rush of new advances, collapsed into such a brief period of time, boggles the mind.

—R. Paul Robertson, MD

Personal Health Maintenance



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—John H. Holbrook, MD

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(Continued from Page 570)

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

October 17—**Annual Cancer Symposium.** Los Alamos. Friday. Contact: Los Alamos Council on Cancer, PO Box 995, Los Alamos 87544.

November 7-8—**New Mexico Medical Society Interim Meeting—"Marketing Strategies for Private Practice" and "Gearing Up for Retirement."** Las Cruces. Friday-Saturday. Holiday Inn de Las Cruces. Contact: New Mexico Medical Society, 303 San Mateo NE, Albuquerque 87108. (505) 266-7868.

November 14-15—**Behavioral/Physiological Changes of Aging.** Albuquerque. Friday-Saturday. Marriott Hotel. Contact: Lovelace Medical Foundation, Office of Medical Education, 2425 Ridgecrest Dr SE, Albuquerque 87108. (505) 262-7000.

December 4-6—**Annual Meeting—New Mexico Chapter, American College of Physicians/New Mexico Society of Internal Medicine.** Thursday-Saturday. AMA Cat. 1. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

January 24-25—**Annual Family Practice Seminar.** Albuquerque. Saturday-Sunday. Marriott Hotel. Contact: New Mexico Chapter, American Academy of Family Physicians, PO Box 23070, Albuquerque 87192. (505) 298-5300.

February 20-22—**15th Annual Taos Lung Disease Symposium.** Taos. Friday-Sunday. Contact: NM Chapter, American Thoracic Society, 216 Truman NE, Albuquerque 87108. (505) 265-0732.

March 5-7—**New Mexico Metabolism Symposium.** Taos. Thursday-Saturday. Quail Ridge Lodge. Contact: Lovelace Medical Foundation, Office of Medical Education, 2425 Ridgecrest Dr SE, Albuquerque 87108. (505) 262-7000.

March 14—**New Mexico Pediatric Society Wylder Lecture—Pediatric Neurology.** Albuquerque. Saturday. Contact: NM Pediatric Society, (505) 758-8651.

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave, Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 W Harvard Ave, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 W Harvard Ave, Roseburg 97470. (503) 673-6641.

Emanuel Hospital, 2801 N Gantenbein St, Portland 97227:

Every Friday, 12:15 p.m. to 1:00 p.m. **Medical Grand Rounds.** Contact: Philippa McClure, Emanuel Hospital, 2801 N Gantenbein St, Portland 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Ave, Portland 97210:

Every Tuesday, 12:00 noon to 1:00 p.m. **Medicine Grand Rounds.** Neurological Sciences Buildings, First Floor Auditorium. Contact: Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Ave, Portland 97201. (503) 229-7454.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder St, Eugene 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene 97440.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

(Continued on Page 574)

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Transamerica Occidental Life Insurance Company*
- Medicare B and Commercial

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- Allstate Life Insurance Company
- The Bankers Life Company
- Benefit Trust Life Insurance Company
- CNA Insurance Companies
- Confederation Life Insurance Company
- Connecticut General Life Insurance Company
- Equitable Life Assurance Society of the U.S.
- The Great-West Life Insurance Company
- Gulf Group Services
- The Hartford Insurance Group
- Hnme Life Insurance Company
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- Medicare B and Cnmmercial

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Colwell Systems	800-637-1140
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EDP Systems, Inc.	405-943-9818
Health America Systems, Inc.	312-362-3730
Independent Computing, Inc.	800-428-2310
MOS, Inc.	800-323-6671
Physicians' Office Computer	213-603-0555
Safeguard Business Systems	800-528-7300
Santiago Data Systems, Inc.	800-652-3500
(In California)	800-435-1222
Univair, Inc. (UNI-CLAIM)	314-426-1099
Westland Software House, Inc.	818-992-0081

Authorized Billing Services

The Morf Organization	415-332-8400

New vendors, billing services and carriers added regularly. For up-to-date list, call 1-800-433-3683, ext. 7321.

(Continued from Page 572)

Salem Hospital, 665 Winter St SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St SE, Salem 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St SE, Salem 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St Vincent Hospital & Medical Center, 9205 SW Barnes Rd, Portland 97225. (503) 297-4411, Ext 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept of Psychiatry, Oregon Health Sciences University, Portland 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept of Medicine, Oregon Health Sciences University, Portland 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland 97201. (503) 225-7590.

EMERGENCY MEDICINE

October 23-24—**Pediatric Advanced Life Support.** Portland. Thursday-Friday. Red Lion Motor Inn/ Portland Center. Contact: OHSU-CME.

November 14-15—**Symposium on Critical Care Medicine.** Portland. Thursday-Friday. Red Lion Motor Inn/Jantzen Beach. Contact: OHSU-CME.

FAMILY PRACTICE

October 23-25—**Pacific Northwest Review of Obstetrics and Gynecology.** See below.

OBSTETRICS AND GYNECOLOGY

October 23-25— **Pacific Northwest Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion Motor Inn/Jantzen Beach. Contact: OHSU-CME.

PEDIATRICS

October 23-24—**Pediatric Advanced Life Support.** Portland. Thursday-Friday. Red Lion Motor Inn/ Portland Center. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

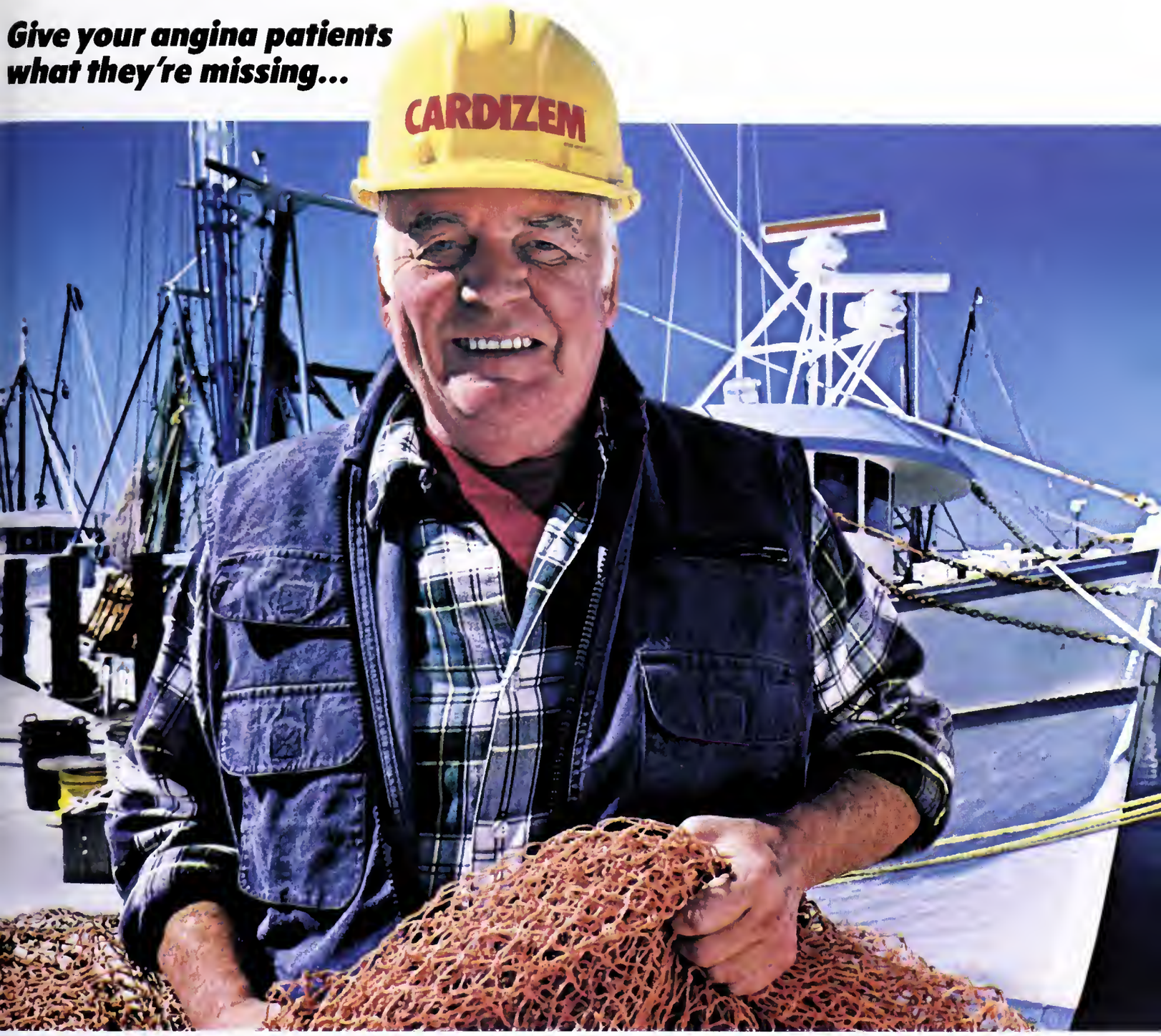
Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

October 31-November 1—**Stress, Emotion and Heart Disease** (Sponsor: UUMC). Friday-Saturday. Marriott Hotel, Salt Lake City. 15 hrs. Contact: Hilmon Castle, MD, (801) 581-8664.

(Continued on Page 577)

Give your angina patients what they're missing...



CARDIZEM®: FEW SIDE EFFECTS

diltiazem HCl/Marion

- ***Antianginal action includes dilatation of coronary arteries, a decrease in vascular resistance/afterload, and a reduction in heart rate***
- ***Proven efficacy when used alone in angina[1]***
- ***Compatible with other antianginals[2,3]****
- ***A safe choice for angina patients with coexisting hypertension, asthma, COPD, or PVD[4,5]***

***See Warnings and Precautions.**

Please see brief summary of prescribing information on the next page.

CARDIZEM® diltiazem HCl/Marion

FEW SIDE EFFECTS IN ANTIANGINAL THERAPY

60 mg tid or qid

Brief Summary
Professional Use Information

CARDIZEM®
(diltiazem HCl) 30 mg and 60 mg Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. ***Cardiac Conduction.*** *CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.*
2. ***Congestive Heart Failure.*** *Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt).*
   Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. ***Hypotension.*** *Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.*
4. ***Acute Hepatic Injury.*** *In rare instances, significant elevations in enzymes such as alkaline phosphatase, CPK, LDH, SGOT, SGPT, and other symptoms consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)*

PRECAUTIONS

General. *CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes, however, these changes were reversible with continued dosing.*

Drug Interaction. *Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)*

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. *A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.*

Pregnancy. *Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.*

There are no well-controlled studies in pregnant women, therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. *Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.*

Pediatric Use. *Safety and effectiveness in children have not been established.*

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	*Angina, arrhythmia, AV block (first degree), AV block (second or third degree — see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.*
Nervous System:	*Amnesia, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.*
Gastrointestinal:	*Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.*
Dermatologic:	*Petechiae, pruritus, photosensitivity, urticaria.*
Other:	*Amblyopia, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.*

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

Issued 7/86

See complete Professional Use Information before prescribing

References: ***1.*** *Pepine CJ, Feldman RL, Hill JA, et al: Clinical outcome after treatment of rest angina with calcium blockers: Comparative experience during the initial year of therapy with diltiazem, nifedipine, and verapamil. Am Heart J 1983, 106(6):1341-1347.* ***2.*** *Shapiro W: Calcium channel blockers: Actions on the heart and uses in ischemic heart disease. Consultant 1984,24(Dec):150-159.* ***3.*** *Johnston DL, Lesowoy R, Humen DP, et al: Clinical and hemodynamic evaluation of propranolol in combination with verapamil, nifedipine and diltiazem in exertional angina pectoris: A placebo-controlled, double-blind, randomized, crossover study. Am J Cardiol 1985,55:680-687.* ***4.*** *Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39.* ***5.*** *Schroeder JS: Calcium and beta blockers in ischemic heart disease: When to use which. Mod Med 1982;50(Sept):94-116.*

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(Continued from Page 574)

November 7-8—**Advanced Trauma Life Support** (Sponsor: UUMC). Friday-Saturday. Quality Inn, Salt Lake City. 16 hrs. Contact: Carla Holmes, (801) 533-6608.

November 20-21—**Postgraduate Laser Program—GI.** (Sponsor: UUMC). Thursday-Friday. University of Utah Medical Center, Salt Lake City. 10 hrs. Contact: John Dixon, MD, (801) 581-2256.

January 5-14—**Hip and Knee Bioskills Workshop** (Sponsor: UUMC). 10 days. Snowbird Resort. 15 hrs. Contact: Aaron Hoffman, MD, (801) 581-8664.

January 20-22—**Pulmonary Function Testing** (Sponsor: UUMC). Tuesday-Thursday. RMCOEH, University of Utah Medical Center. 18 hrs. Contact: Connie Crandall, (801) 581-8719.

February 1-6—**Diagnostic Imaging/Interventional Radiology** (Sponsor: UUMC). Sunday-Friday. Snowbird Resort. 20 hrs. Contact: Judy Gallegos, (801) 581-8188.

February 10-13—**Family Practice Refresher Course** (Sponsor: UUMC). Tuesday-Friday. Westin Hotel Utah, Salt Lake City. 28 hrs. Contact: Denise Denton, (801) 581-5224.

February 11-14—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wednesday-Saturday. Salt Lake City. 17 hrs. Contact: (801) 521-1221.

February 12-14—**Rigid Fixation Techniques/Craniomaxillofacial Surgery** (Sponsor: UUMC). Thursday-Saturday. Snowbird Resort. 20 hrs. Contact: Louis Morales, MD, (801) 581-8664.

February 14-21—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). One week. Park City Resort. 25 hrs. Contact: John Matsen, MD, (801) 581-7480.

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143, (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

February 16-20—**Surgical Pathology Workshops** (Sponsor: UUMC). Monday-Friday. Park City Resort. 20 hrs. Contact: Tom Colby, MD, (801) 581-7480.

February 19-21—**Mid-Winter Trauma Seminar for Military and Civilians** (Sponsor: UUMC). Thursday-Saturday. Westin Hotel Utah, Salt Lake City. 15 hrs. Contact: Clayton Petty, MD, (801) 581-6393.

February 20-24—**Postgraduate Course in Anesthesiology** (Sponsor: UUMC). Friday-Tuesday. Salt Lake City. 16 hrs. Contact: Theodore Stanley, MD, (801) 581-6393.

February 21-25—**Annual Ob-Gyn Update** (Sponsor: UUMC). Saturday-Wednesday. Park City. 15 hrs. Contact: James Scott, MD, (801) 581-5501.

February 22-27—**Park City Dermatology Seminar** (Sponsor: UUMC). Sunday-Friday. Park City. 18 hrs. Contact: Gerald Kruegar, MD, (801) 581-7837.

February 25-28—**Gynecologic Oncology** (Sponsor: UUMC). Wednesday-Saturday. Park City. 15 hrs. Contact: James Scott, MD, (801) 581-5501.

February 26-28—**Arthroscopic Surgery** (Sponsor: UUMC). Thursday-Saturday. Westin Hotel Utah, Salt Lake City. 21 hrs. Contact: Robert Metcalf, MD, (801) 581-7601.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

October 15—**Diagnostic Imaging.** Seattle. Wednesday. Contact: NW Hospital, 1550 N 115 St, Seattle 98133. (206) 364-0500, ext 1621.

October 15—**Legal Aspects of Occupational Health.** Seattle. Wednesday. Center for Occupational Health and Safety. Contact: U/W.

October 17-18—**Alternative Delivery Systems: Strategies for Physician Control.** Washington, D.C. Friday-Saturday. Contact: American Society of Internal Medicine, (202) 289-1700.

October 24—**Twentieth Annual Cancer Conference: Lung Cancer.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

October 24-25—**Sinus Surgery.** Seattle. Friday-Saturday. U/W Health Sciences. Contact: U/W.

October 29-30—**Focus: Critical Care.** Tacoma. Wednesday-Thursday. Contact: College of Medical Education-Tacoma.

November 6-7—**Current Concepts in Drug Therapy.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

November 7—**Symposium on the Diabetic Foot.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

November 12—**Pain Management.** Seattle. Wednesday. Contact: NW Hospital, 1550 N 115 St, Seattle 98133. (206) 364-05000, ext 1621.

November 12-14—**Washington ACEP Scientific Assembly—Topics in Emergency Medicine.** Seattle. Wednesday-Friday. Westin Hotel. Contact: American College of Emergency Physicians, (206) 441-9762.

November 12-14—**Ventilation: Principles and Applications.** Seattle. Wednesday-Friday. NW Center for Occupational Health and Safety. Contact: U/W.

November 21-22—**Short-Term Therapy.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

December 3-5—**Molecular Medicine.** Seattle. Wednesday-Friday. Urban Horticulture Center. Contact: U/W.

December 5—**Practical Pediatrics.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

December 5-6—**Northwest Urologists/Washington State Urology—1986 Annual Meeting.** Tacoma. Friday-Saturday. Tacoma Sheraton. Contact: WSMA.

January 15-16—**Agricultural Health and Safety.** Seattle. Thursday-Friday. NW Center for Occupational Health and Safety. Contact: U/W.

January 23—**Topics in Pulmonary Medicine: Interstitial Lung Disease.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

February 4-6—**Spirometry Training for Worker Screening.** Seattle. Wednesday-Friday. NW Center for Occupational Health and Safety. Contact: U/W.

February 6-7—**Modern Concepts in Allergy.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 7-8—**Vocational Rehabilitation.** Bellevue. Saturday-Sunday. Contact: U/W.

February 20-21—**Office Gynecology for the Primary Care Physician.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 26-27—**Health and Safety of Firefighters.** Seattle. Thursday-Friday. NW Center for Occupational Health and Safety. Contact: U/W.

March 13—**Recent Developments in Occupational Medicine.** Seattle. Friday. NW Center for Occupational Health and Safety. Contact: U/W.

March 20—**Neuro-Opthalmology Seminar.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

March 30-April 10—**Rehabilitation Review.** Seattle. Monday-Friday. Stouffer Madison Hotel. Contact: U/W.

April 15—**Introduction to Industrial Hygiene.** Seattle. Wednesday. NW Center for Occupational Health and Safety. Contact: U/W.

April 17—**Basic Monitoring Laboratory.** Seattle. Friday. NW Center for Occupational Health and Safety. Contact: U/W.

April 19—**Flexible Sigmoidoscopy.** Bellevue. Sunday. Overlake Hospital Medical Center. Contact: Nancy Aziz, OHMC, 1035-116th NE, Bellevue 98004. 454-4011, ext 2969.

April 25—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 20-22—**Family Violence.** Seattle. Wednesday-Friday. Seattle Center. Contact: U/W.

WYOMING

February 28-March 7, 1987—**Selected Topics in Wilderness and Environmental Medicine.** A nordic skiing adventure at Yellowstone National Park. One week. Sponsors: University of Arizona, Department of Family and Community Medicine, and Epic Medical Expeditions. 24 hrs. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995. ◆

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50. Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 623-4801.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

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ARIZONA BASED PHYSICIAN RECRUITMENT firm has opportunities Coast to Coast. "Professionals working with Professionals." Over 14 years experience. Call (602) 795-7474; or send CV to: Mitchell & Associates, Inc., 2761 N. Country Club Rd., Ste. 202, Tucson, AZ 85716.

OB/GYN: Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, Administration, 1400 East Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

GYNECOLOGIST—Needed in Ketchum/Sun Valley multispecialty clinic. Excellent climate, unlimited recreation facilities and very good schools. Income dependent on productivity. Dr Bryan Stone, PO Box 2198, Ketchum, ID 83340; (208) 726-9361.

ORTHOPEDIC SURGEON, OB/GYN, FP AND IM physicians needed throughout the United States. Excellent solo and group opportunities for BC/BE physicians. Call (602) 795-7474 or send CV to Mitchell & Associates, Inc., 2761 N. Country Club Rd., Ste 202, Tucson, AZ 85716.

RURAL COLORADO, OB/GYN: BC/BE OB/GYN to join three FPs, three Internists, and General Surgeon with growing group. Guaranteed salary and fringes plus incentives. Excellent opportunity for person interested in rural living, mountain recreation, health care delivery for underserved populations. Full- or part-time position. Send CV to Michael Bloom, 204 Carson Ave., Alamosa, CO 81101; (303) 589-5161.

OBSTETRICS AND GYNECOLOGY—multispecialty, family care oriented group has two excellent practice opportunities for OB/GYN specialists. We are located in a growing, dynamic Southwest city and offer an excellent benefit and incentive salary program. Send CV to D. R. Molesworth, Administrator, The Tucson Clinic, P.C., PO Box 26926, Tucson, AZ 85726.

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NORTHERN CALIFORNIA, Emergency Medicine—Full-time positions available in the Emergency Room at The University of California, Davis, Medical Center. The University serves a large region of Northern California and is a major trauma center. Emergency physicians teach and supervise medical students and housestaff in addition to treating patients, primarily. Opportunities exist for involvement in other School of Medicine teaching activities. Applicants should send curriculum vitae to Robert W. Derlet, MD, University of California Davis Medical Center, 2315 Stockton Blvd, Department of Emergency Medicine, Trailer 1219, Sacramento, CA 95817.

MD NEEDS—SOUTHERN CALIFORNIA ONLY—FPs, GP, IM, OB/GYN, OR and other subspecialties needed for private groups and associations. Baker, Ellerd and Associates, Inc., 16200 Ventura Blvd., Ste. 426, Encino, CA 91436; call (818) 995-4311.

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WANTED—Family Physician or Internist with interest in preventive medicine to share 1,400 square foot medical suite in beautiful medical office complex. Contact John O. Lawder, MD, 23441 Madison St., #110, Torrance, CA 90505; (213) 373-9768.

EMERGENCY MEDICINE/FAMILY PRACTICE. We are seeking BP/BC physician to join our group in Denver. Multiple practice opportunities including hospital, ED and FEC. Please send CV and salary history to Western Physician, PO Box 18451, Denver, CO 80218.

SURGEON—General Surgeon needed to serve Casa Grande Regional Medical Center, a 100 bed, general and acute care hospital opened in 1984. Please send CV to: Administrator, Casa Grande Regional Medical Center, 1800 E. Florence Blvd., Casa Grande, AZ 85222.

PHYSICIANS WANTED

FAMILY PRACTICE—Multispecialty family care oriented group needs additional Family Practice Physicians. Excellent practice opportunity in a dynamic Southwest city; good benefits and salary plan. Send CV to: D. R. Molesworth, Administrator, The Tucson Clinic, P.C., PO Box 26926, Tucson, AZ 85726.

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VANCOUVER/CAMAS, WASHINGTON. BC/BE Family Practitioner to join a growing FP department within a well established 30-physician multispecialty group. Satellite clinic is in a high growth area with a multitude of outstanding recreational, cultural and educational opportunities in nearby Portland, Oregon, Mt. Hood, and the Columbia Gorge. High quality practice with excellent vacation and benefits package. Salary first two years, with potential for full partnership. Send CV to: Roger R. Garretson, 700 N.E. 87th Ave., Vancouver, WA 98664.

NORTHERN CALIFORNIA: BE/BC General Internist needed immediately to join 18-physician Internal Medicine Department in a large private multispecialty group. Competitive salary, liberal fringe benefits and early corporate membership. Respond by telephone to Physician Recruiting at (408) 282-7944.

IMMEDIATE OPENING—Immediate Care Center. Large, multispecialty clinic located in southeastern Washington has an opening for a qualified physician to join a Board certified Emergency Physician in staffing a walk in/immediate care center. Corporate paid retirement plan, excellent compensation package, superior recreational and cultural opportunities in a family-oriented environment. Send complete CV to James Mercer, MD, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362; or call 1-(509) 522-0550.

NORTHERN SAN FRANCISCO BAY AREA—Seeking physician Board certified or eligible in IM for Internist position in growing department of medicine. Competitive salary and excellent benefits. Call or write: Chief, Dept. of Medicine, Kaiser Permanente Medical Center, 1550 Gateway Blvd., Fairfield, CA 94533; phone (707) 427-4200.

INVASIVE/NON-INVASIVE CARDIOLOGIST, BC/BE to join busy cardiology department of multispecialty group in Central California. Send CV to: David J. Cislowski, MD, FACC, 222 W. Willow St., Visalia, CA 93291.

ORTHOPEDIC SURGEON—Board certified—California license to perform disability evaluations on a part- or full-time basis. Ideal for retirement income supplement. Respond to Frances MacMorran (619) 296-6226.

ALLERGIST/CLINICAL IMMUNOLOGIST (Pediatric and Adult) BE/BC to join a well established allergist working in an 80 plus physician multispecialty group located in California's Central Valley. Within two hours of San Francisco, Yosemite, Carmel and the Sierras. Generous guaranteed base salary with incentive, early partnership. Reply with CV and references to: C. R. Maino, MD, Gould Medical Foundation, 600 Coffee Rd., Modesto, CA 95355.

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(Continued on Page 582)

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(Continued from Page 580)

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BUSY FEMALE GYN looking for quality associate. Excellent opportunity in suburban Los Angeles for BC/BE OB/GYN. Full- or part-time. Gynecology only, but great potential for full Obstetrics practice if desired. Position available immediately. Must be sensitive, well-trained, personable, and hard-working man or woman. Please reply to Number 152, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PEDIATRICIAN—Seeking pediatrician to serve the communities of Central Pinal County. Casa Grande Regional Medical Center is a 100 bed, 1984 constructed general and acute care hospital. Please send CV to: Administrator, Casa Grande Regional Medical Center, 1800 E. Florence Blvd., Casa Grande, AZ 85222.

FAMILY PRACTICE PHYSICIAN—Casa Grande Regional Medical Center is recruiting a family practice physician to serve a growing community in Central Pinal County. Casa Grande Regional Medical Center is a 100 bed, 1984 constructed general and acute care hospital. Please send CV to: Administrator, Casa Grande Regional Medical Center, 1800 E. Florence Blvd., Casa Grande, AZ 85222.

FAMILY PHYSICIAN for growing innovative family health center in San Francisco Bay Peninsula. Practice OB and newborn to geriatrics. No major surgery. Health education emphasis. Multidisciplinary team. POMR. Abundant education and teaching opportunity. Ideal living. ABFP certified residency preferred. Women applicants encouraged. EOE. Salary negotiable. Contact: J. Hopkins, MD, 704 Webster, Palo Alto, CA 94301; (415) 324-1940.

CALIFORNIA. BC/BE Pediatrician and Internist to join young group at the edge of the Sierras. Send CV to Number 149, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ENDOCRINOLOGIST needed for partnership in flourishing private practice in beautiful southwestern city. Reply Number 151, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NEW MEXICO, ALBUQUERQUE: Full-time, career-oriented position available in New Mexico's largest hospital system. Prefer ER residency trained or Family Practice, Internal Medicine with ER Board eligibility. Competitive salary, pension/profit sharing, and excellent benefits. Albuquerque has multiple and varied cultural advantages. Please send CV to: Robert C. Henry, MD, Presbyterian Hospital, 1100 Central SE, Albuquerque, NM 87102.

DIABETOLOGIST NEEDED: January 1988 to join large solo diabetes center practice. Exclusive consultative endocrinology practice. Desirable Pacific Northwest college town. Submit CV to Number 150, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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ASSISTANT PROFESSOR OF MEDICINE, RHEUMATOLOGY. The Department of Medicine, University of California, San Francisco is expanding its program in rheumatology and immunology at the San Francisco General Hospital and seeks candidates for a full-time position as Assistant Professor of Medicine. Applicants should have both interest and ability in immunology and/or related fields of laboratory research that are pertinent to rheumatic diseases. Demonstrated excellent in clinical care and teaching are required, as are certification in Internal Medicine and eligibility for certification in Rheumatology. Candidates should send a curriculum vitae, and the names of three individuals to be contacted for references, to Ira M. Goldstein, MD, University of California, Box 0868, Third and Parnassus Avenues, San Francisco, CA 94143-0868. UCSF is an affirmative action employer. Women and minorities are encouraged to apply.

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Position available—Wheeler Hospital Emergency/Outpatient Service, Gilroy, California. 22,000 patient visits per year. Pleasant community, good schools, churches, recreation. Fifty minutes to Monterey, ninety minutes to San Francisco. Contact:

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Wheeler Hospital, 651 W. Sixth St., Gilroy, CA 95020
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CARDIOLOGIST NEEDED—BC/BE relocating or new fellow to join associates at regional medical center in scenic northern Rocky Mountain area. The right individual must possess superior invasive and noninvasive skills, a caring approach towards patients, and a willingness to work hard as a team player. Reply with letter and CV to Number 153, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PEDIATRICIAN: The San Luis Medical Clinic, Ltd. a 35-member multispecialty group practicing on the California Central Coast has an immediate need for a general Pediatrician. Full range of benefits and all practice costs paid. Send CV to: Colin J. Wells, MD, San Luis Medical Clinic Ltd., 1235 Osos St., San Luis Obispo, CA 93401-3619. No telephone calls please.

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ARIZONA—VA Medical Center, Prescott, Arizona, Medical Service is recruiting for a full-time, Board certified Geriatrician and/or General Internist. Position available now. Prescott is a 217 bed general medical hospital with an active medical service, ICU/CCU, Ambulatory Care, Rehabilitation Medicine Service, Alcohol Dependency Treatment Program, and intermediate bed care units. Prescott is located in the mountains of North Central Arizona with a population of 25,000. Salary range is $70,000 to $80,000 depending on qualifications. Send curriculum vitae to: F. C. Lepperd, Jr., MD, Chief of Staff, VA Medical Center, Prescott, AZ 86313; or call (602) 445-4860, Ext. 301; Equal Opportunity Employer.

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Western States Physician Services
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(209) 297-7748

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FAMILY PRACTICE. Position available with 35-member multispecialty group; BC/BE; immediate opening; full range of benefits plus immediate shareholder status; excellent opportunity; Central Coast of California. Respond with CV to: Colin J. Wells, MD, San Luis Medical Clinic, Ltd., 1235 Osos St., San Luis Obispo, CA 93401-3619. No phone calls please.

NEW MEXICO—Primary Care Physician for 600-bed psychiatric/geriatric hospital in Las Vegas, New Mexico. Competitive salaries and generous benefits including on-call compensation. Superb climate and nearby recreational facilities. Contact: Medical Director, Las Vegas Medical Center, PO Box 1388, Las Vegas, NM 87701-1388 or call (505) 425-6711, ext. 5402.

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In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

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Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

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The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published Pages should be numbered consecutively, beginning with the title page. Manuscripts produced with a dot-matrix printer are ordinarily not acceptable.

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Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

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The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

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Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

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Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)" and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

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It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

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(Continued from Page 582)

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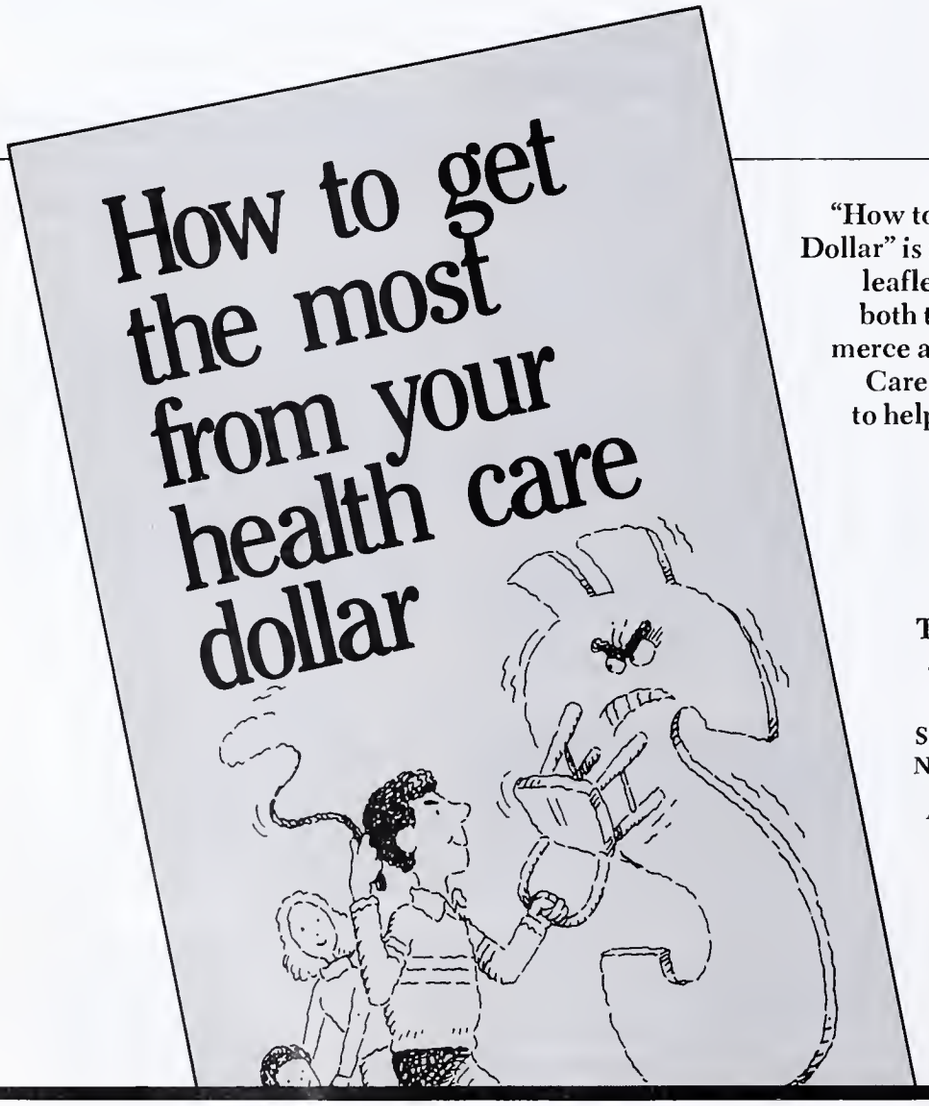

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California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 863-5522. Annual Meeting: March 6-11, 1987, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1987: Date and place to be announced.

Hawaii Medical Association—320 Ward Ave, Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1986, Westin Ilikai Hotel, Honolulu.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 27-August 2, 1987, Coeur d'Alene.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Interim Meeting: April 3-4, 1987, Colonial Inn, Helena.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 30-May 3, 1987, Ormsby House, Carson City.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 6-8, 1987, Clarion Four Seasons, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): April 3-4, 1987, Salishan Lodge, Lincoln City.

Utah State Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1987: Date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: 1987: Date and place to be announced.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 25-29, 1987, Jackson Lake Lodge, Moran.

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Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).
***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).
Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady state concentrations of the tricyclic drugs. Concomitant use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.
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Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.
Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.
Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.
Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.
Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.
Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.
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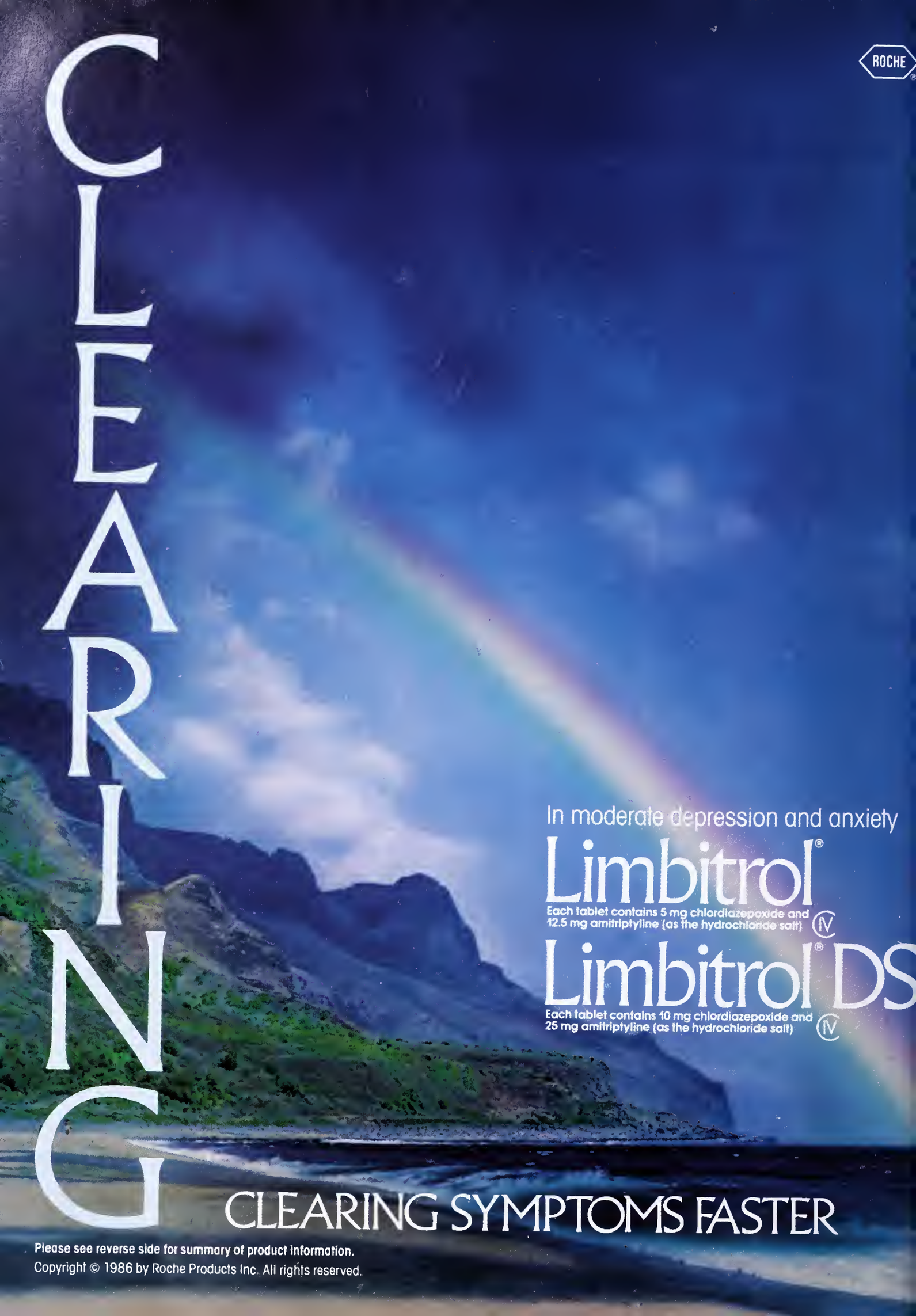

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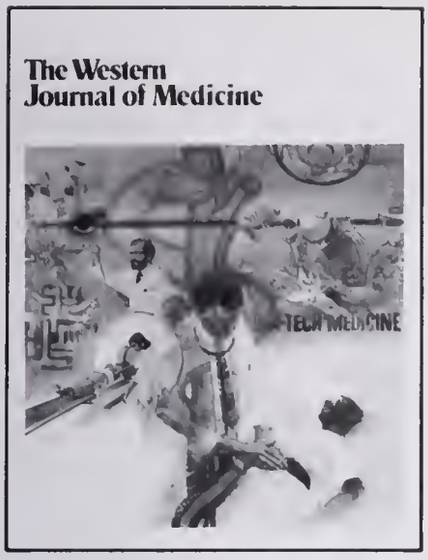

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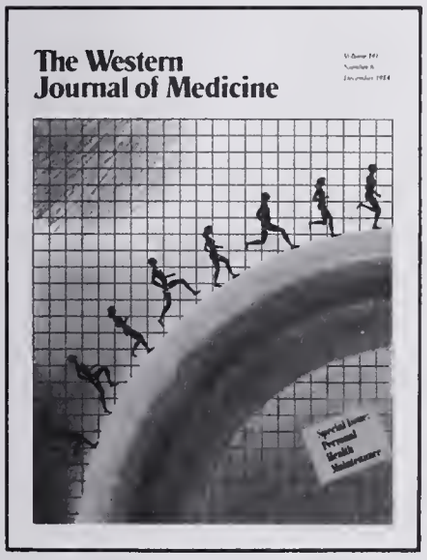

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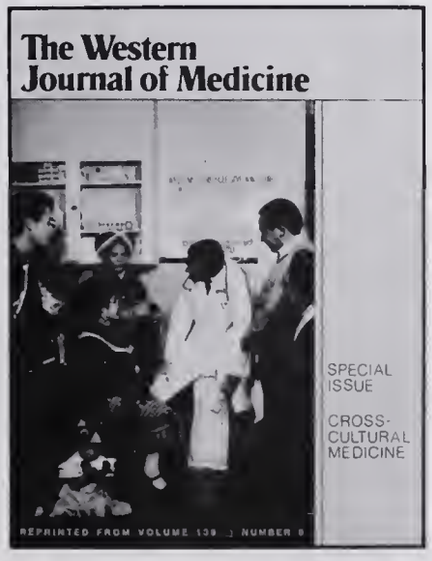

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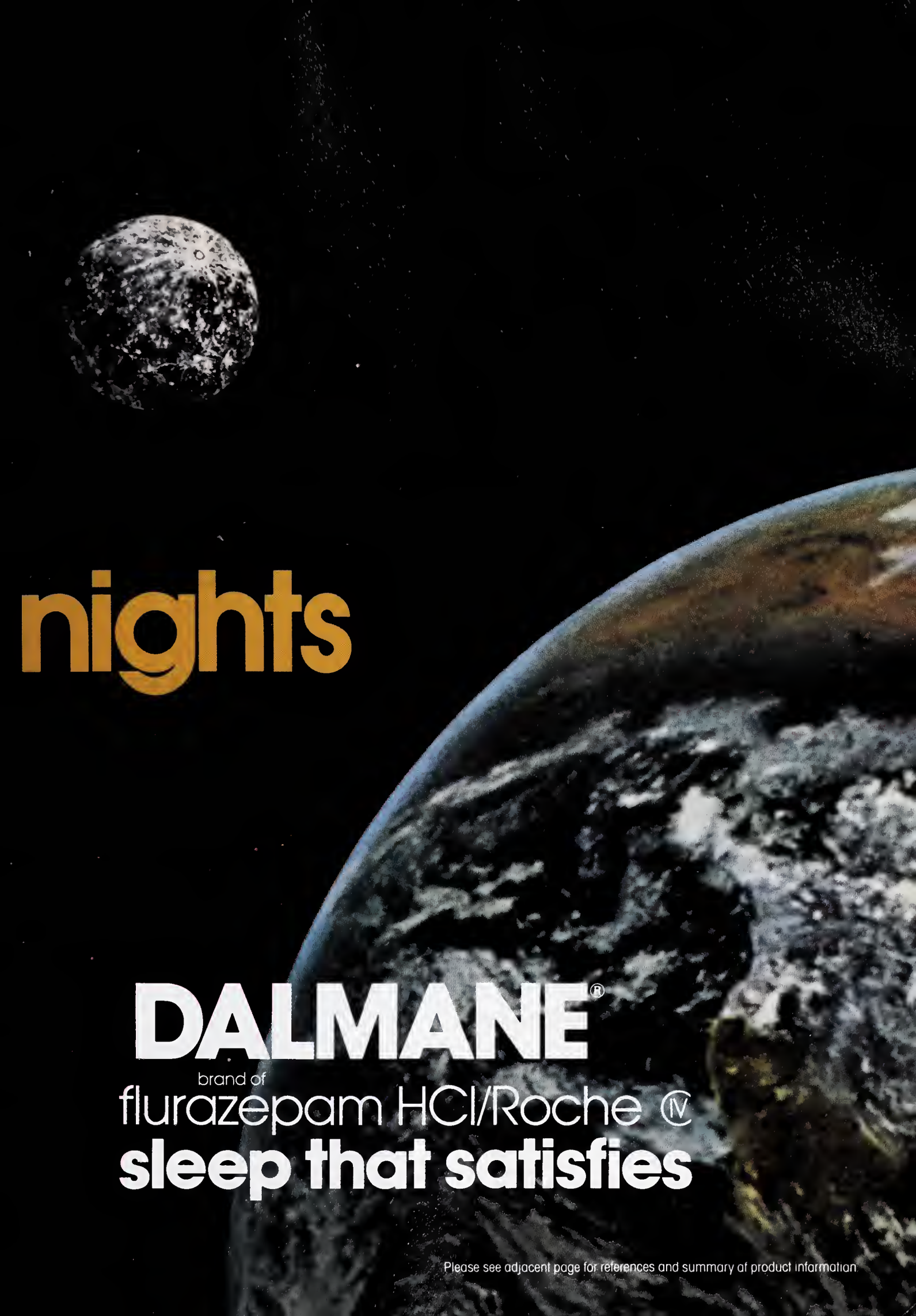
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Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.
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□ **Increases ability to exercise.**
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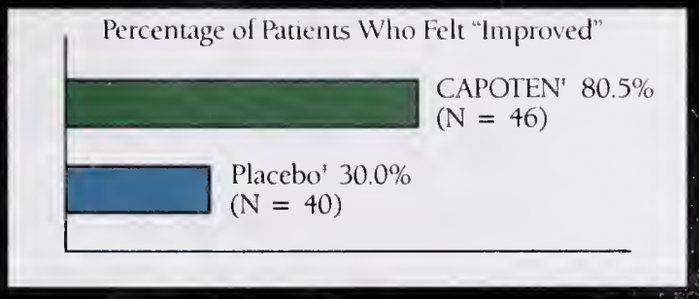

□ *Use CAPOTEN when symptoms persist despite digitalis and diuretic therapy.*

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CAPOTEN® (captopril tablets) IN HEART FAILURE§

YOUR FIRST CHOICE AFTER DIGITALIS AND DIURETICS

*Angiotensin Converting Enzyme

†Ninety-two patients, refractory to but continuing on digitalis and diuretics, were given CAPOTEN or placebo for 12 weeks. Patients were primarily New York Heart Association Class II and Class III. Dosages of CAPOTEN ranged from an initial 25 mg tid to a maximum maintenance dosage of 100 mg tid.[1]

‡Given with digitalis and diuretics.

§CAPOTEN is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis. In using CAPOTEN, consideration should be given to the risk of neutropenia/agranulocytosis. Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs (e.g., procainamide) known to affect the white cells or immune response. Evaluation of heart failure patients should always include assessment of renal function. See INDICATIONS, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension—CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Neutropenia/Agranulocytosis—Neutropenia ($<1000/mm^3$) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine <1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. Of reported cases, about half had serum creatinine ≥1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count $<1000/mm^3$) withdraw captopril and closely follow the patient's course.

Proteinuria—Total urinary proteins >1 g/day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy, patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function,* Hypertension—Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction.

Surgery/Anesthesia—If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity—In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis—Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C—There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal—About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis have occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic—Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension may occur, see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—About 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg also available in bottles of 1000), and in UNIMATIC® single dose packs of 100 tablets. (J3-658D)

Reference: 1 Cannon PJ, Cnley JM, Dzau VJ, et al: A placebo-controlled tnal of captopnl in refractory chronic congestive heart failure. J Am Col Cardiol 2:755–763, 1983

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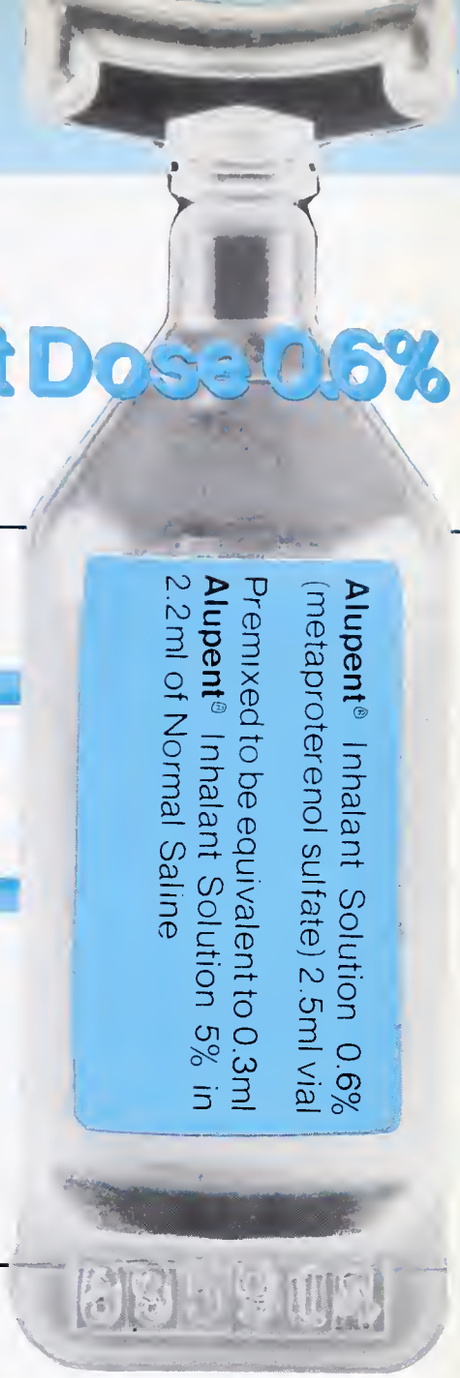

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Bronchodilator

ıief Summary of Prescribing Information

DICATIONS AND USAGE Alupent® (metaproterenol sulfate) Inhalant olution is indicated as bronchodilator for bronchial asthma and for versible bronchospasm which may occur in association with bronchitis d emphysema

ONTRAINDICATIONS Use in patients with cardiac arrhythmias asso- ated with tachycardia is contraindicated

hough rare, immediate hypersensitivity reactions can occur. Therefore, upent (metaproterenol sulfate) Inhalant Solution, 0 6% is contraindicated patients with a history of hypersensitivity to any of its components.

ARNINGS Excessive use of adrenergic aerosols is potentially dan- rous Fatalities have been reported following excessive use of Alupent ietaproterenol sulfate) as with other sympathomimetic inhalation eparations, and the exact cause is unknown Cardiac arrest was noted several cases

radoxical bronchoconstriction with repeated excessive administration s been noted with sympathomimetic agents.

tients should be advised to contact their physician in the event that they not respond to their usual dose of sympathomimetic amine aerosol

ECAUTIONS Because Alupent (metaproterenol sulfate) Inhalant Solu- n is a sympathomimetic drug, it should be used with great caution in tients with hypertension, coronary artery disease, congestive heart ure, hyperthyroidism or diabetes, or when there is sensitivity to sympa- omimetic amines

ormation for Patients Extreme care must be exercised with respect to administration of additional sympathomimetic agents A sufficient erval of time should elapse prior to administration of another sympatho- metic agent

rcinogenesis Long-term studies in mice and rats to evaluate the oral rcinogenic potential of metaproterenol sulfate have not been completed udies of metaproterenol sulfate have not been conducted to determine utagenic potential or effect on fertility

egnancy *Teratogenic Effects: Pregnancy Category C* Alupent (meta- proterenol sulfate) has been shown to be teratogenic and embryocidal in rabbits when given orally in doses 620 times the human inhalation dose. There are no adequate and well-controlled studies in pregnant women Alupent should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Oral reproduction studies in mice, rats and rabbits showed no teratogenic or embryocidal effects at 50 mg/kg corresponding to 310 times the human inhalation dose Teratogenic effects in the rabbit included skeletal abnormalities and hydrocephalus with bone separation

Nursing Mothers It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Alupent (metaproterenol sulfate) is administered to a nursing woman.

Pediatric Use Safety and effectiveness in children below the age of 12 have not been established

ADVERSE REACTIONS Adverse reactions are similar to those noted with other sympathomimetic agents.

The most frequent adverse reactions to Alupent (metaproterenol sulfate) are nervousness and tachycardia which occur in about 1 in 7 patients, tremor which occurs in about 1 to 20 patients and nausea which occurs in about 1 in 50 patients Less frequent adverse reactions are hypertension, palpitations, vomiting and bad taste which occur in approximately 1 in 300 patients.

HOW SUPPLIED Alupent (metaproterenol sulfate) Inhalant Solution Unit Dose Vials are supplied as 0 6% clear colorless or nearly colorless solution, each vial containing 2 5 ml, with 25 vials per box Do not use the solution if it is brown or has a precipitate.

Consult package insert before prescribing AL-UD-BPI-5/86

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The Western Journal of Medicine

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EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

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CORGARD®
(nadolol tablets)

Preserves renal blood flow

CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: CORGARD (nadolol) is a synthetic non-selective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect; monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 years oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy Category C—In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE—For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg q.d. (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg q.d. (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and in Unimatic® unit-dose packs of 100 tablets. The 40 mg, 80 mg, and 120 mg potencies are also available in bottles of 1000 tablets. (J3-527E)

References: 1. Alexander JC, Christie MH, Vernam KA, et al: Long-term experience with nadolol in treatment of hypertension and angina pectoris. Am Heart J 108:1136-1140, 1984.

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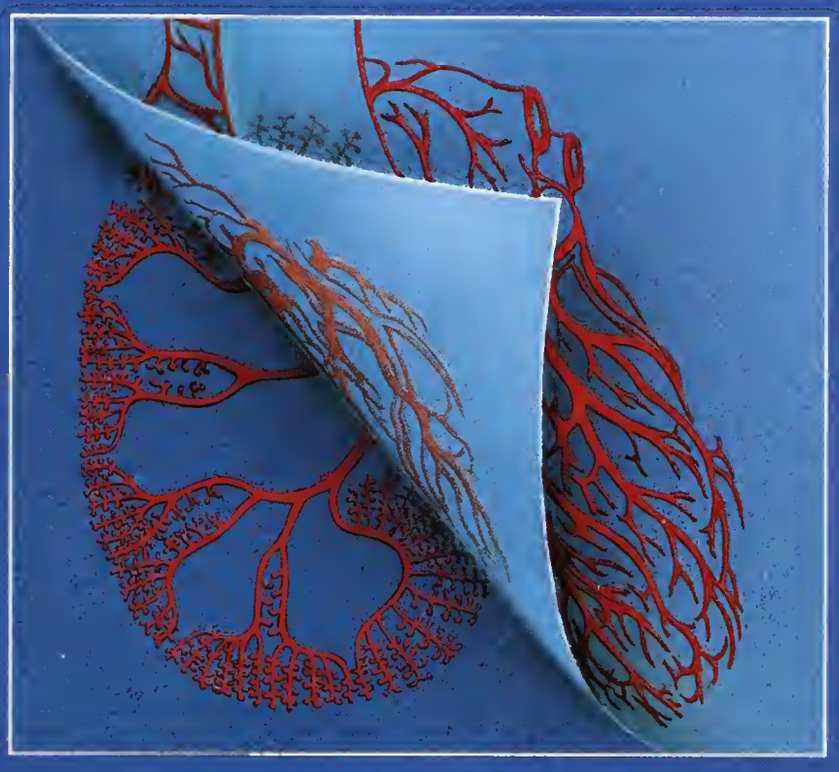
Issued: August, 1986

IN THE HYPERTENSIVE PATIENT

CORGARD®
(nadolol tablets)

PRESERVES RENAL BLOOD FLOW...

AN UNDERLYING PHARMACOLOGIC CONSIDERATION



By preserving renal blood flow, CORGARD can minimize the compensatory sodium and water retention which may aggravate hypertension.

In a 2-year study of 106 hypertensive patients treated with CORGARD, serum creatinine, an indicator of renal function, decreased 20% from baseline.[1]

CORGARD®
(nadolol tablets)
Preserves renal blood flow

PRINCETON PHARMACEUTICAL PRODUCTS
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Extra strength
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J-6138 January 1986

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geriatrics...
Anxiety and
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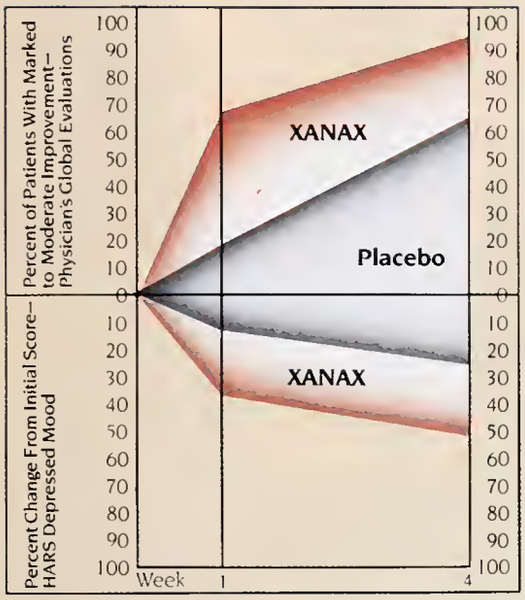
symptoms
go hand
in hand.

Xanax effectively relieves anxiety with associated depressive symptoms.



In a recent clinical study[1] of 83 geriatric patients with clinical anxiety, 73% were diagnosed as having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than does placebo in reducing the Hamilton Anxiety Rating Scale Total Score and individual items, including depressed mood (see Figure).

With clinical advantages for geriatric patients.

- Effectively relieves the symptoms of anxiety
- Also relieves anxiety with associated depressed mood
- Well tolerated—side effects, if they occur, are generally observed at the beginning of therapy and usually disappear with continued medication. Drowsiness and light-headedness were the most commonly reported adverse reactions
- Does not cause cardiovascular toxicity
- **Specific geriatric dosage**—0.25 mg, two or three times daily

1. Cohn JB. Double-blind safety and efficacy comparison of alprazolam and placebo in the treatment of anxiety in geriatric patients. *Curr Ther Res* 1984;35(1):100-112.

Xanax® 0.25 mg Tablets

alprazolam C-IV

Upjohn 100 A Century of Caring 1886·1986

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Kalamazoo, Michigan 49001, USA

Please see adjacent page for brief summary of prescribing information

XANAX® Tablets
(alprazolam) ℞

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, eg, drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes of unknown significance have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

B-4-S

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I-5963
January 1986

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A GREAT WAY TO SERVE

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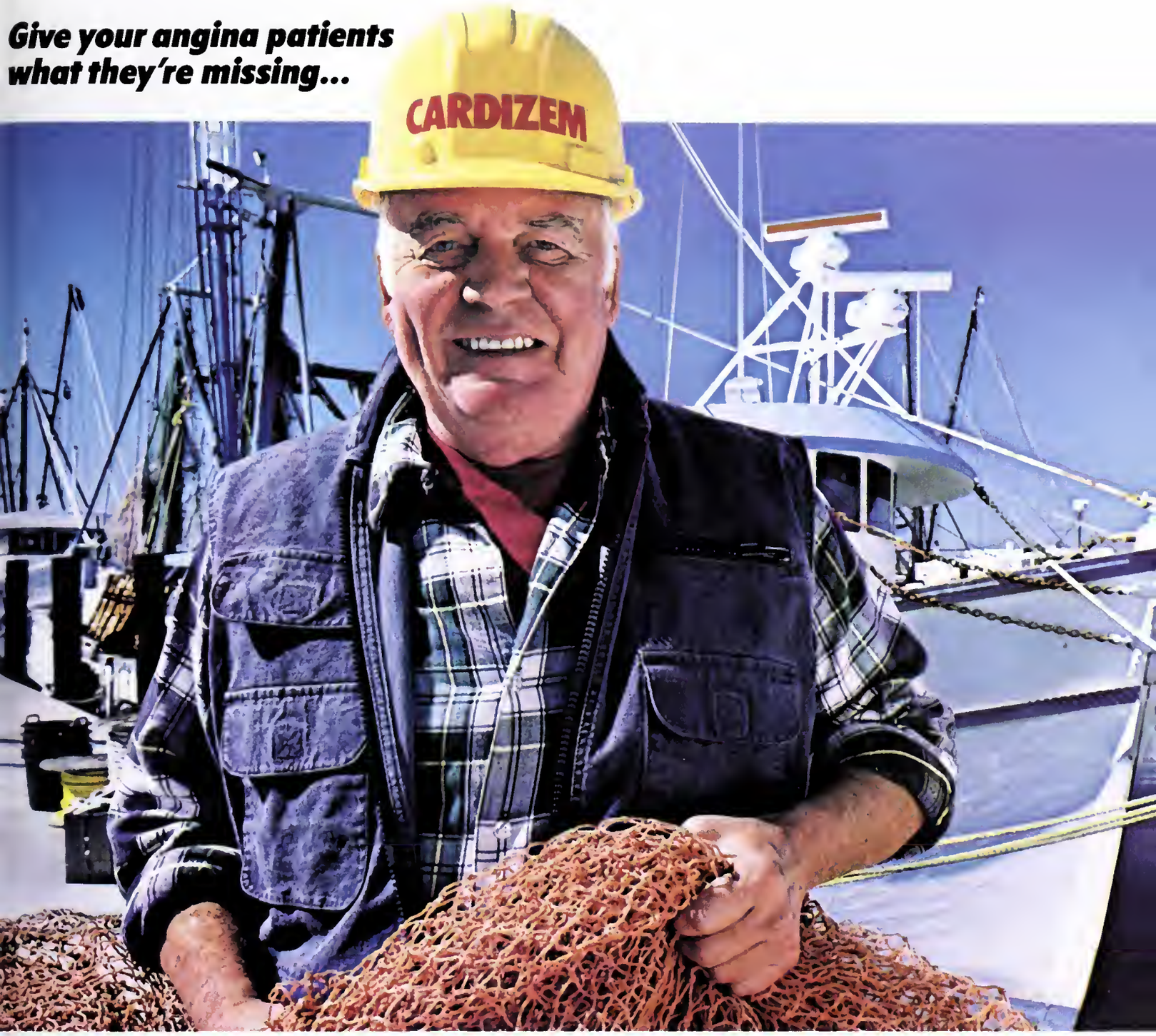


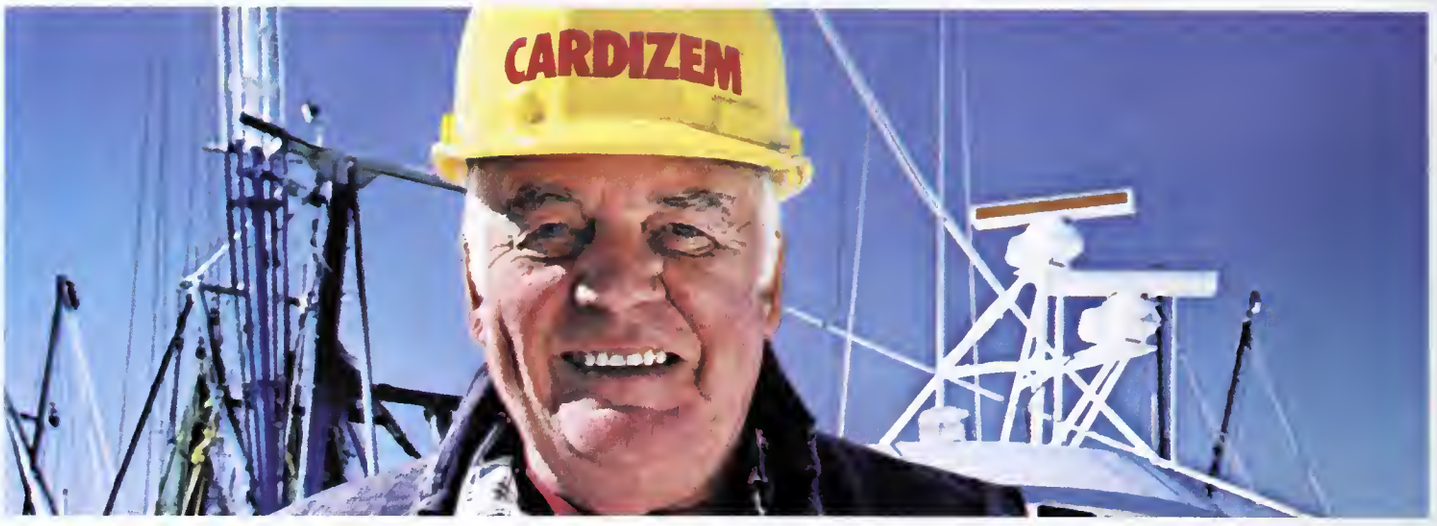
CARDIZEM®: FEW SIDE EFFECTS

diltiazem HCl/Marion

- ***Antianginal action includes dilatation of coronary arteries, a decrease in vascular resistance/afterload, and a reduction in heart rate***
- ***Proven efficacy when used alone in angina[1]***
- ***Compatible with other antianginals[2,3*]***
- ***A safe choice for angina patients with coexisting hypertension, asthma, COPD, or PVD[4,5]***

***See Warnings and Precautions.**

Please see brief summary of prescribing information on the next page.



CARDIZEM® FEW SIDE EFFECTS IN ANTIANGINAL THERAPY

diltiazem HCl/Marion

60 mg tid or qid

Brief Summary
Professional Use Information

CARDIZEM®
(diltiazem HCl) 30 mg and 60 mg Tablets

CONTRAINDICATIONS
CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. ***Cardiac Conduction.*** *CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.*
2. ***Congestive Heart Failure.*** *Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt).*
   Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. ***Hypotension.*** *Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.*
4. ***Acute Hepatic Injury.*** *In rare instances, significant elevations in enzymes such as alkaline phosphatase, CPK, LDH, SGOT, SGPT, and other symptoms consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)*

PRECAUTIONS
General. *CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.*

Drug Interaction. *Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)*

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. *A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.*

Pregnancy. *Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.*

There are no well-controlled studies in pregnant women, therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. *Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.*

Pediatric Use. *Safety and effectiveness in children have not been established.*

ADVERSE REACTIONS
Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	*Angina, arrhythmia, AV block (first degree), AV block (second or third degree — see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope*
Nervous System:	*Amnesia, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.*
Gastrointestinal:	*Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase*
Dermatologic:	*Petechiae, pruritus, photosensitivity, urticaria*
Other:	*Amblyopia, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties*

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

Issued 7/86

See complete Professional Use Information before prescribing

References: ***1.*** *Pepine CJ, Feldman RL, Hill JA, et al: Clinical outcome after treatment of rest angina with calcium blockers. Comparative experience during the initial year of therapy with diltiazem, nifedipine, and verapamil. Am Heart J 1983, 106(6):1341-1347.* ***2.*** *Shapiro W: Calcium channel blockers. Actions on the heart and uses in ischemic heart disease. Consultant 1984,24(Dec):150-159.* ***3.*** *Johnston DL, Lesaway R, Humen DP, et al: Clinical and hemodynamic evaluation of propranolol in combination with verapamil, nifedipine and diltiazem in exertional angina pectoris: A placebo-controlled, double-blind, randomized, crossover study. Am J Cardiol 1985;55:680-687.* ***4.*** *Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39.* ***5.*** *Schroeder JS: Calcium and beta blockers in ischemic heart disease: When to use which. Mod Med 1982;50(Sept):94-116.*

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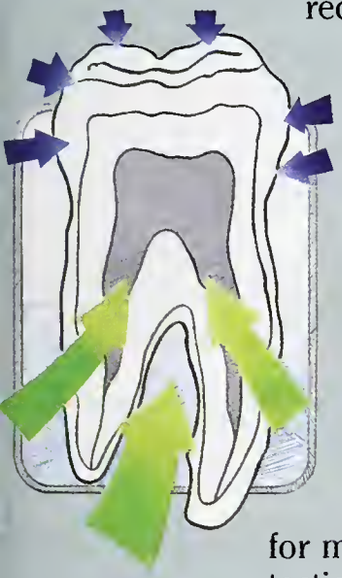

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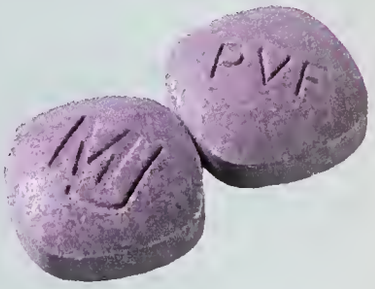

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REFERENCES:
[1]Aasenden R and Peebles T: Effects of Fluoride Supplementation From Birth on Human Deciduous and Permanent Teeth. Arch Oral Biol 19:321, 1974.
[2]Hambert L: Controlled Trial of Fluoride in Vitamin Drops for Prevention of Caries in Children. Lancet Feb. 27, 1971, p. 442.
[3]Newbrun, E.: How Fluoride Works: Topical vs. Systemic Action, in Mead Johnson Clinical Report Series, Clinical Importance of Fluoride Nutrition in Infants, Children and Young Adults, Chicago, Pragmaton®, 1985, p. 7.

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INDICATIONS AND USAGE: Prophylaxis of vitamin deficiencies and dental caries in children and adults when fluoride of water supply does not exceed 0.7 ppm.[1,2,3] And, in the case of TRI-VI-FLOR® 0.25 mg Drops with Iron and POLY-VI-FLOR® Drops and Chewable Tablets with Iron, prophylaxis against iron deficiencies. Note: VI-FLOR Drops do not contain folic acid because the vitamin is not stable in liquid form.

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Keep all VI-FLOR with Iron products tightly closed and away from direct light.

VI-FLOR Drops should be dispensed in the original plastic container, since contact with glass leads to instability and precipitation.

ADVERSE REACTIONS: Allergic rash has rarely been reported

DOSAGE AND ADMINISTRATION:

Supplemental Fluoride Dosage Schedule (mg/day)*

Age	Concentration of Fluoride in Drinking Water (ppm)		
	<0.3	0.3-0.7	>0.7
2 wk-2 yr**	0.25	0	0
2-3 yr	0.5	0.25	0
3-16 yr	1.0	0.5	0

*From the American Academy of Pediatrics Committee on Nutrition statement, Fluoride Supplementation: Revised Dosage Schedule. Pediatrics 63(1):150-152, 1979.

**The Committee favors initiating fluoride supplementation shortly after birth in breast-fed infants (0.25 mg F/day). In formula-fed infants, fluoride supplementation should be according to the fluoride content of the water used to prepare formula.

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POLY-VI-FLOR 0.5 mg with Iron	Tablets	Bottle of 100	0.5
POLY-VI-FLOR 1.0 mg	Tablets	Bottle of 100	1.0
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1. Hennon DK, Stookey GK and Muhler JC: The Clinical Anticariogenic Effectiveness of Supplementary Fluoride-Vitamin Preparations—Results at the End of Four Years. J Dentistry for Children 34:439-443 (Nov) 1967.
2. Hennon DK, Stookey GK and Muhler JC: The Clinical Anticariogenic Effectiveness of Supplementary Fluoride-Vitamin Preparations—Results at the End of Five and a Half Years. Pharmacology and Therapeutics in Dentistry 1:1-6 (Oct) 1970.
3. Hennon DK, Stookey GK and Muhler JC: Prophylaxis of Dental Caries: Relative Effectiveness of Chewable Fluoride Preparations With and Without Added Vitamins. J Pediatrics 80:1018-1021 (June) 1972.

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Books Received

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CONTRACEPTION AND CHRONIC ILLNESSES: A CLINICIAN'S SOURCEBOOK—Lawrence S. Neinstein, MD, Associate Professor, Clinical Pediatrics and Medicine, University of Southern California School of Medicine, Los Angeles, and Barbara Katz, MD, a pediatrician in private practice, Bricktown, New Jersey. American Health Consultant Books, 67 Peachtree Park Drive, NE, Atlanta, GA 30309, 1986. 88 pages, $49.95 (paperback).

DUPUYTREN'S DISEASE—Second English Edition—Edited by J. T. Hueston, MD(Melb), FRCS (Eng), Melbourne, and R. Tubiana, Paris. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 210 pages, $58.

ECTOPIC PREGNANCY—Edited by Alan H. DeCherney, MD, John Slade Ely Professor of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut. Aspen Publishers Inc, 1600 Research Blvd, Rockville, MD 20850, 1986. 132 pages, $28.50.

ESSENTIALS OF UROLOGY—Edited by Joseph N. Corriere, Jr, MD, Professor of Surgery (Urology): Associate Chairman, Department of Surgery, and Director, Division of Urology, University of Texas Medical School at Houston. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 332 pages, $33 (paperback).

GENITOURINARY ULTRASOUND—Volume 18 in Clinics in Diagnostic Ultrasound—Edited by Hedvig Hricak, MD, Associate Professor of Radiology and Urology, Department of Radiology, University of California, San Francisco, School of Medicine. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 286 pages, $39.

GETTING RID OF PATIENTS—CONTRADICTIONS IN THE SOCIALIZATION OF PHYSICIANS—Terry Mizrahi, Associate Professor of Social Work, Hunter College, City University of New York. Rutgers University Press, 109 Church St, New Brunswick, NJ 08901, 1986. 215 pages, $27.

HARD CHOICES—MIXED BLESSINGS OF MODERN MEDICAL TECHNOLOGY—B. D. Colen. G. P. Putnam's Sons, 200 Madison Ave, New York, NY 10016, 1986. 264 pages, $18.95.

HEPATIC TRANSPLANTATION—ANESTHETIC AND PERIOPERATIVE MANAGEMENT—Edited by Peter M. Winter, Professor and Chairman, and Yoo Goo Kang, MD, Assistant Professor, Department of Anesthesiology, University of Pittsburgh School of Medicine. Praeger, 521 Fifth Ave, New York, NY 10175, 1986. 255 pages, $39.95.

THE HISTORY OF SCURVY AND VITAMIN C—Kenneth J. Carpenter, PhD, Professor of Nutrition, University of California, Berkeley, and formerly Fellow of Sidney Sussex College and Reader in Nutrition, University of Cambridge, England. Cambridge University Press, 32 E 57th St, New York, NY 10022, 1986. 278 pages, $39.50

KEY FACTS IN HISTOLOGY—Ray C. Henrikson, PhD, Associate Professor of Anatomy, and Gordon I. Kaye, PhD, Professor and Chairman of Anatomy and Professor of Pathology, Albany Medical College, Albany, NY. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 439 pages, $33 (paperback).

LIGAMENT INJURIES AND THEIR TREATMENT—Edited by D. H. R. Jenkins, MB, ChB, ChM, FRCS, Consultant Orthopaedic Surgeon, Cardiff Royal Infirmary, Cardiff, Wales. Aspen Publishers Inc, 1600 Research Blvd, Rockville, MD 20850, 1985. 343 pages, $40.

LIVER SURGERY—Volume 12 in CLINICAL SURGERY INTERNATIONAL—Edited by Stig Bengmark, MD, Director and Professor of Surgery, Lund University, Lund, Sweden, and L. H. Blumgart, MD, FRCS, Director and Professor of Surgery, Royal Postgraduate Medical School, Hammersmith Hospital, London. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 181 pages, $57.

LYMPH NODE BIOPSY INTERPRETATION—Edited by A. G. Stansfeld, MA, MB, BChir (Cantab), Department of Histopathology, St Bartholomew's Hospital, London. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 399 pages, $96.

MANUAL OF OUTPATIENT GYNECOLOGY—Edited by Carol Havens, MD, Clinical Assistant Professor, Dept of Family Practice, and Nancy D. Sullivan, FNP, Clinical Instructor, Dept of Family Practice, University of California, Davis, School of Medicine, and Patti Tilton, MD, Resident Physician, Dept of Obstetrics and Gynecology, University of California Davis Medical Center, Sacramento. Little, Brown and Company, 34 Beacon St, Boston, MA 02106, 1986. 258 pages, $17.50 (spiral bound).

THE MEDICARE SYSTEM OF PROSPECTIVE PAYMENT—IMPLICATIONS FOR MEDICAL EDUCATION AND PRACTICE—Edited by Mohan L. Garg, ScD, Professor, and Barbara M. Barzansky, PhD, Associate Professor, Center for Educational Development, University of Illinois at Chicago. Praeger Publishers, 521 Fifth Ave, New York, NY 10175, 1986. 222 pages, price not given.

MEETINGS BETWEEN EXPERTS—AN APPROACH TO SHARING IDEAS IN MEDICAL CONSULTATIONS—David Tuckett, Mary Boulton, Coral Olson and Anthony Williams. Tavistock Publications, 29 W 35th St, New York, NY 10001, 1986. 283 pages; $37.50 (cloth bound), $16.95 (paperback).

MENTAL DISABILITY IN AMERICA SINCE WORLD WAR II—Don Martindale, PhD, and Edith Martindale, RN. Philosophical Library, 200 W 57th St, New York, NY 10019, 1986. 286 pages, $15.

NEUROANATOMY—A CONCEPTUAL APPROACH—C. Romero-Sierra, MD, DSc, Professor, Department of Anatomy, Queen's University, Kingston, Ontario, Canada. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 422 pages, $23 (paperback).

NONINVASIVE RESPIRATORY MONITORING—Volume 3 in CONTEMPORARY ISSUES IN PULMONARY DISEASE—Edited by Michael L. Nochomovitz, MD, Assistant Professor of Medicine, and Neil S. Cherniack, MD, Professor of Medicine and Chief, Division of Pulmonary Medicine, Case Western Reserve University School of Medicine, Veterans Administration Medical Center, Cleveland. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 221 pages, $35.

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

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February 25-27—**Tenth Annual Mid-Winter Symposium in OB/GYN.** Scottsdale Hilton, Scottsdale. Wednesday-Friday. Contact: Maricopa Medical Center, (602) 267-5444.

February 26-28—**Neurology and Neurosurgery of the Aging.** Mountain Shadows Resort, Scottsdale. Thursday-Saturday. Contact: Barrow Neurological Institute, (602) 285-3178 or (800) BARROW1.

March 4-8—**11th Annual Valley of the Sun Dermatologic Symposium.** Loews Paradise Valley Resort, Scottsdale. Wednesday-Sunday. Contact: Millard Thaler, MD, 2055 E Southern, #B, Tempe 85282.

March 11-13—**Them Ol' Bones.** Wednesday-Friday. Contact: Christine Campbell for St Luke's Medical Center, (602) 947-7756.

March 17-20—**Pediatric Update—1987.** La Posada Resort, Scottsdale. Tuesday-Friday. Contact: Phoenix Children's Hospital, (602) 239-4350.

March 19-21—**23rd Annual Arizona Chest Symposium.** Doubletree Hotel, Tucson. Thursday-Saturday. Contact: Sandy Younker-Hellman, RN, U of A, (602) 327-5461.

March 21-22—**13th Annual James H. McDonald Urological Seminar.** Sheraton Scottsdale Resort, Scottsdale. Saturday-Sunday. Contact: Maricopa Medical Center, (602) 267-5371.

April 6-8—**Practical Cardiology for the Family Physician.** La Posada Resort, Scottsdale. Monday-Wednesday. Contact: American College of Cardiology, (301) 897-5400, ext 226.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

PATHOLOGY

November 15-16—**Tumors of the Thyroid Gland and Head and Neck Tumors.** Arizona Society of Pathologists and U of A at Scottsdale Hilton, Scottsdale. Saturday-Sunday. 7 hrs. Contact: Beverly Richter, Arizona Society of Pathologists, 810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901.

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From the System Sciences Department, the Rand Corporation, Santa Monica, California, and the Department of Psychiatry, Neuropsychiatric Institute, and School of Public Health, School of Medicine, UCLA, Los Angeles. Dr Goldberg is now with the Health Data Institute, Inc, Lexington, Massachusetts.

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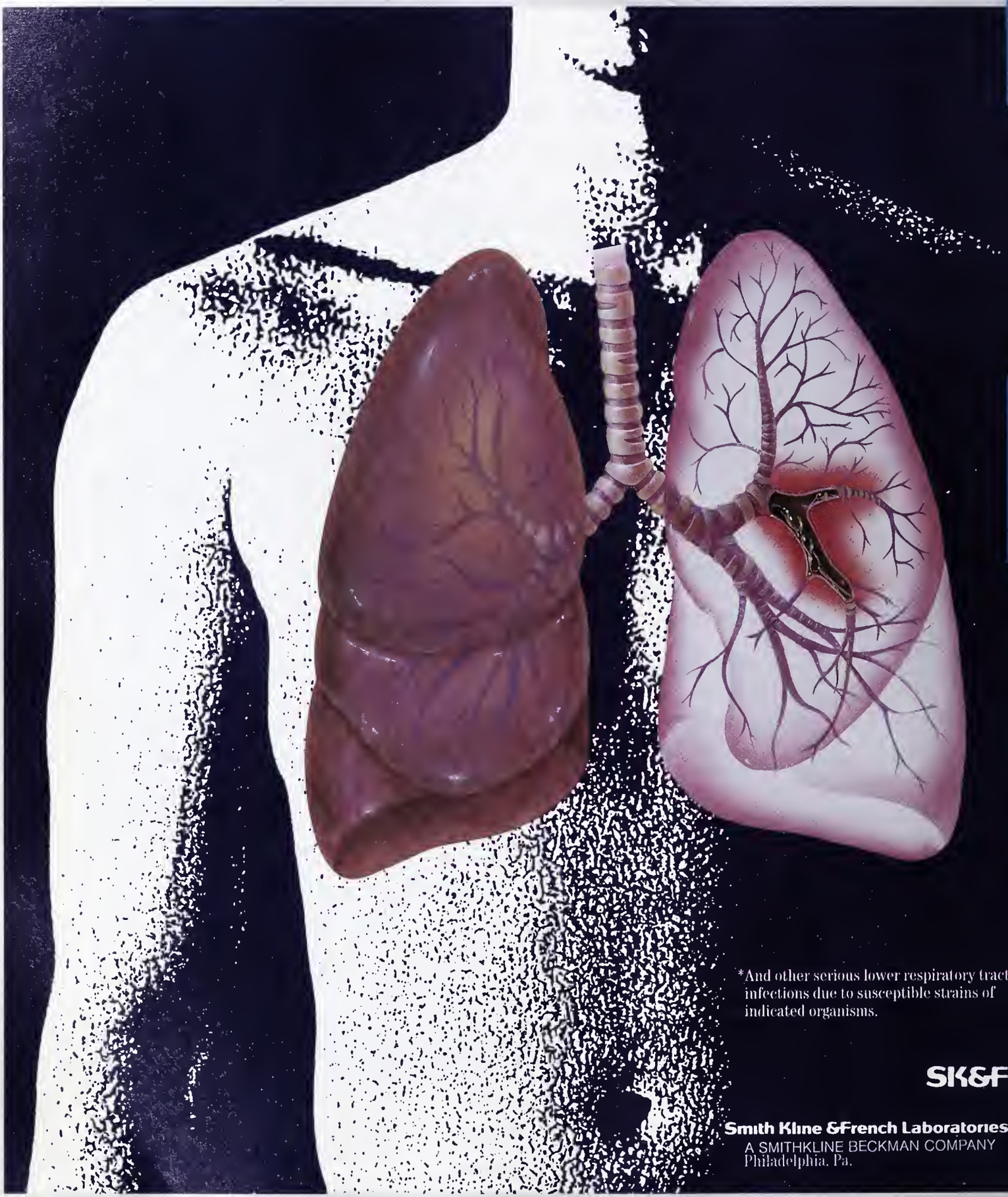
★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

In Pneumonia*... The



*And other serious lower respiratory tract infections due to susceptible strains of indicated organisms.

SK&F

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'Monocid' Advantage

The Benefits of Once-Daily Dosing

- 24-Hour Coverage of Common Pathogens
- Effective Against Ampicillin-Resistant *H. influenzae*
- I.V. or I.M.: Hospital or Outpatient Management
- Lowest Cost per Course of Therapy[1-4]

Plus The Efficacy You Expect

- 95% Clinical Success (91% cured,* 4% improved) with Once-Daily Dosing[5-7]

Once-a-Day/Broad-Spectrum

MONOCID®

IV/IM

brand of sterile

cefonicid sodium

(lyophilized)

*Since the definition of "cure" may vary significantly among clinical settings and investigators, the reader is urged to consult the references cited.

Before prescribing, please consult the brief summary of 'Monocid' prescribing information on the following page.

Once-a-Day Therapy in

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MONOCID®

IV/IM brand of sterile

cefonicid sodium

(lyophilized)

The 'Monocid' Advantage
The Benefits of Once-Daily Dosing
Plus the Efficacy You Expect

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

INDICATIONS AND USAGE

Monocid (sterile cefonicid sodium, SK&F) is indicated in the treatment of infections due to susceptible strains of the microorganisms listed below:

LOWER RESPIRATORY TRACT INFECTIONS, due to *Streptococcus pneumonioe* (formerly *D. pneumonioe*); *Klebsiella pneumonioe*; *Escherichia coli*; and *Hemophilus influenzoe* (ampicillin-resistant and ampicillin-sensitive).

URINARY TRACT INFECTIONS, due to *Escherichia coli*; *Proteus mirobilis* (indole-negative *Proteus*); and *Klebsiella pneumoniae*.

SKIN AND SKIN STRUCTURE INFECTIONS, due to *Stophylococcus oureus* and *S. epidermidis*; *Streptococcus pyogenes* (Group A *Streptococcus*) and *S. ogoloctioe* (Group B *Streptococcus*).

SEPTICEMIA, due to *Streptococcus pneumonioe* (formerly *D. pneumoniae*) and *Escherichio coli*.

BONE AND JOINT INFECTIONS, due to *Stophylococcus aureus*.

Therapy with 'Monocid' may be initiated pending results of susceptibility studies. Treatment should be adjusted according to findings.

SURGICAL PROPHYLAXIS

Administration of a single 1 gram dose of 'Monocid' before surgery may reduce the incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (e.g., colorectal surgery, vaginal hysterectomy, or cholecystectomy in high-risk patients), or in patients in whom infection at the operative site would present a serious risk (e.g., prosthetic arthroplasty, open heart surgery). Although cefonicid has been shown to be as effective as cefazolin in prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery or prosthetic heart valve replacement.

In cesarean section, the use of 'Monocid' (after the umbilical cord has been clamped) may reduce the incidence of certain postoperative infections.

When administered one hour prior to surgical procedures for which it is indicated, a single 1 gram dose of 'Monocid' provides protection from most infections due to susceptible organisms throughout the course of the procedure and for approximately 24 hours after administration. Intraoperative and postoperative administration of 'Monocid' is not necessary. Daily doses of 'Monocid' may be administered for two additional days in patients undergoing prosthetic arthroplasty or open heart surgery.

Before using 'Monocid' concomitantly with other antibiotics, the prescribing information for those agents should be reviewed for contraindications, warnings, precautions and adverse reactions. Renal function should be carefully monitored.

CONTRAINDICATIONS

'Monocid' is contraindicated in persons who have shown hypersensitivity to cephalosporin antibiotics.

WARNINGS

BEFORE THERAPY WITH 'MONOCID' IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider that diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics alters normal flora of the colon and may permit overgrowth of Clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance and when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should also be considered.

PRECAUTIONS

General: With any antibiotic, prolonged use may result in overgrowth of nonsusceptible organisms. Careful observation is essential, and appropriate measures should be taken if superinfection occurs.

Drug Interactions: Nephrotoxicity has been reported following concomitant administration of other cephalosporins and aminoglycosides.

Pregnancy: (Category B.) Reproduction studies have been performed in mice, rabbits and rats at doses up to an equivalent of 40 times the usual adult human dose and have revealed no evidence of impaired fertility or harm to the fetus due to 'Monocid'. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.

Labor and Delivery: In cesarean section, 'Monocid' should be administered only after the umbilical cord has been clamped.

Nursing Mothers: 'Monocid' is excreted in human milk in low concentrations. Caution should be exercised when 'Monocid' is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

Beta-lactam antibiotics with methyl-thio-tetrazole side chains have been shown to cause testicular atrophy in prepubertal rats, which persisted into adulthood and resulted in decreased spermatogenesis and decreased fertility. Cefonicid, which contains a methylsulfonic-thio-tetrazole moiety, has no adverse effect on the male reproductive system of prepubertal, juvenile or adult rats when given under identical conditions.

ADVERSE REACTIONS

'Monocid' is generally well tolerated and adverse reactions have occurred infrequently. The most common adverse reaction has been pain on I.M. injection. On-therapy conditions occurring in greater than 1% of 'Monocid'-treated patients were:

Injection Site Phenomena (5.7%): Pain and/or discomfort on injection; less often, burning, phlebitis at I.V. site.

Increased Plotelets (1.7%).

Increosed Eosinophils (2.9%).

Liver Function Test Alterations (1.6%): Increased alkaline phosphatase, increased SGOT, increased SGPT, increased GGTP, increased LDH.

Less frequent on-therapy conditions occurring in less than 1% of 'Monocid'-treated patients were:

Hypersensitivity Reoctions: Fever, rash, pruritus, erythema, myalgia and anaphylactoid-type reactions have been reported.

Hematology: Decreased WBC, neutropenia, thrombocytopenia, positive Coombs' test.

Diarrhea.

DOSAGE AND ADMINISTRATION

General

The usual adult dosage is 1 gram of 'Monocid' given once every 24 hours, intravenously or by deep intramuscular injection. Doses in excess of 1 gram daily are rarely necessary; however, in exceptional cases dosage of up to 2 grams given once daily have been well tolerated. When administering 2 gram I.M. doses once daily, one-half the dose should be administered in different large muscle masses.

Surgical Prophylaxis

When administered one hour prior to appropriate surgical procedures (see Indications and Usage), a 1 gram dose of 'Monocid' provides protection from most infections due to susceptible organisms throughout the course of the procedure and for approximately 24 hours after administration. Intraoperative and postoperative administration of 'Monocid' is not necessary. Daily doses of 'Monocid' may be administered for two additional days in patients undergoing prosthetic arthroplasty or open heart surgery.

In cesarean section 'Monocid' should be administered only after the umbilical cord has been clamped.

General Guidelines for Dosage of 'Monocid', I.V. or I.M.

Type of Infection	Daily Dose (grams)	Frequency
Uncomplicated Urinary Tract	0.5	once every 24 hours
Mild to Moderate	1	once every 24 hours
Severe or Life-Threatening	2*	once every 24 hours
Surgical Prophylaxis	1	1 hour preoperatively

*When administering 2 gram I.M. doses once daily, one-half the dose should be administered in different large muscle masses.

Impaired Renal Function

Modification of 'Monocid' dosage is necessary in patients with impaired renal function. Before prescribing, consult Dosage and Administration section of complete prescribing information.

HOW SUPPLIED

'Monocid' is supplied in vials equivalent to 500 mg. and 1 gram of cefonicid; in "Piggyback" Vials for I.V. admixture equivalent to 1 gram of cefonicid; and in Pharmacy Bulk Vials equivalent to 10 grams of cefonicid.

BRS-MC:L15 Date of issuance Feb. 1986

References:

1 Report from International Health Services, Ltd., Jan.-Mar., 1986.
2. Report from Health Information Programs, Inc., Jan.-June, 1985.
3. Smeeding, J.E.: Cost Analysis of Second-Generation Cephalosporins and Economic Implications of Decreased Frequency of Administration, *Adv. Ther.* 2:260-267 (Sept.-Oct.) 1985.
4. Correspondence from Tom C. Snader Consultants, Inc., April 1986.
5. Geckler, R.W., et al.: *Rev. Infect. Dis.* 6:S847-S852, (Nov.-Dec.) 1984
6. Wallace, R.J., Jr., et al.: *Antimicrob. Agents Chemother.* 21 231-235 (Feb.) 1982.
7. Simelaro, J.P., et al.: *Adv. Ther.* 2:192-202 (Sept.-Oct.) 1985.

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CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

December 21-27—**Allergy, Immunology and the Practicing Physician—"Christmas '86—Maui."** Hawaii Medical Association at Royal Lahaina Resort, Kaanapali Beach, Maui. One week. 18 hrs. Fee: $385. Contact: Joe Harrison, MD, Symposium Maui, Inc, PO Box 10185, Lahaina, HI 96761. (808) 879-8182 or 661-8032.

February 11-14—**Immunology and the Clinical Practice of Allergy.** UCSD at San Diego Hilton Beach and Tennis Resort. Wednesday-Saturday. 20 hrs. Contact: UCSD

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

ANESTHESIOLOGY

January 8-11—**Anesthesia Update—1987.** UCSD at Hotel Inter-Continental, San Diego. Thursday-Sunday. 20 hrs. Contact: UCSD.

January 30—February 1—**25th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Marriott Hotel, Los Angeles. Friday-Sunday. 15 hrs. Fee: $175. Contact: Wayne Herbert, MD, Children's Hospital of Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

February 8-12—**15th Obstetric Anesthesia Conference.** Ohio State University Hospital at Sheraton Waikiki Hotel, Hawaii. Sunday-Thursday. Contact: Ohio State University Hospital, Dept of Anesthesiology, 410 W 10th Ave, Columbus, OH 43210. (614) 421-8487.

March 21-22—**Los Angeles County Society of Anesthesiologists 32nd Postgraduate Assembly.** Los Angeles Hilton Hotel. Saturday-Sunday. Contact: LA County Society of Anesthesiologists, 333 S Beverly Dr, Ste 111, Beverly Hills 90212. (213) 556-8865.

April 27-May 1—**California Society of Anesthesiologists Hawaiian Seminar.** Sheraton Kauai Hotel, Poipu Beach, Hawaii. Monday-Friday. 20 hrs. Contact: Linda P. Londerville, CSA, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

CANCER

December 5-6—**Recent Advances in Occupational Cancer.** UCSF at Cathedral Hill Hotel, San Francisco. Friday-Saturday. 13 hrs. Fee: $200. Contact: UCSF.

February 16-18—**Clinical Hematology and Oncology—1987.** Scripps Clinic, La Jolla at Vacation Village Resort, San Diego. Monday-Wednesday. Contact: Bonny Mower, Dept of Academic Affairs, Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

March 12-14—**2nd International Conference on Monoclonal Antibody Immunoconjugates for**

Cancer. UCSD at Hotel Inter-Continental, San Diego. Thursday-Saturday. Contact: UCSD.

March 18-20—**7th Annual Current Approaches to Radiation Oncology, Biology and Physics.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday. 18 hrs. Fee: $275-325. Contact: UCSF

April 3—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Friday. 7 hrs. Fee: $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

April 5—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Newporter Hotel, Newport Beach. Sunday. Fee: $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

CARDIOLOGY

December 5-6—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Bally's (MGM) Grand Hotel, Las Vegas, Nevada. Friday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

December 5-7—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Caesars Palace, Las Vegas, Nevada. Friday-Sunday. 13 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

December 12-13—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Americana Canyon Hotel, Palm Springs. Friday-Saturday. 11 hrs. Fee: $295. Contact: Medical Education Resources, Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or in Colorado (303) 798-9682.

December 12-14—**Advances in Heart Disease.** American College of Cardiology at Hyatt Regency on Union Square, San Francisco. Friday-Sunday. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 227.

January 23-25—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

January 29-31—**Cardiology '87.** Scripps Memorial Hospital, La Jolla at La Jolla Marriott Hotel, San Diego. Thursday-Saturday. 18 hrs. Fee: $275. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 29-31—**Clinical Nuclear Cardiology: Case Review with the Experts.** American College of Cardiology at Cedars-Sinai Medical Center, Los Angeles. Thursday-Saturday. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400.

February 4-7—**4th Annual Cardiopulmonary Conference.** American College of Chest Physicians at Lake Tahoe. Wednesday-Saturday. Contact: ACCP, 911 Busse Highway, Park Ridge, IL 60068. (312) 698-2200 or (916) 739-8833.

February 5-8—**Pathophysiology and Techniques of Cardiopulmonary Bypass: VII.** Cardiothoracic Research and Education Foundation at Sheraton Island East Hotel, San Diego. Thursday-Sunday. 15 hrs. Fee: $300. Contact: CREF, PO Box 33185, San Diego 92103. (619) 692-9115.

February 6-7—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Bally's (MGM) Grand Hotel, Las Vegas, Nevada. Friday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

February 9-13—**2nd Annual Cardiovascular Conference.** American College of Cardiology at Sheraton Royal Waikaloa Hotel, Kona Coast, Hawaii. Monday-Friday. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 227.

February 13-14—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Americana Resort Hotel, Palm Springs. Friday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

March 22-25—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Royal Lahaina Hotel, Maui, Hawaii. Sunday-Wednesday. 13 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

March 27-28—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Desert Inn Hotel, Las Vegas, Nevada. Friday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

April 10-11—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Inter-Continental Hotel, San Diego. Friday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

(Continued on Page 620)

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Downtown San Francisco
Suite 415

(Continued from Page 618)

DERMATOLOGY

January 23-25—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** Continuing Medical Education Associates, San Diego. Friday-Sunday. 20 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

EMERGENCY MEDICINE

November 16—**Emergencies in Medical Practice.** Granada Hills Community Hospital at Sheraton Universal Hotel, North Hollywood. Sunday. 7 hrs. Fee: $100. Contact: Beverly Chaussee, Granada Hills Community Hospital, 10445 Balboa Blvd, Granada Hills 91344. (818) 360-1021, ext 6789.

December 7-13—**Current Concepts in Emergency Care.** American College of Emergency Physicians at Royal Lahaina Resort, Maui. Sunday-Saturday. 25 hrs. Contact: Georgine Elich, Kailani World Travel, 4192 Meridian Ave, Bellingham, WA 98226. USA (800) 426-2561 or in Washington (800) 562-2597.

December 8-12—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD. Monday-Friday. 32 hrs. Fee: $325-440. Contact: UCSD.

January 12-16—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD at San Diego Hilton Hotel. Monday-Friday. 32 hrs. Fee: $325-440. Contact: UCSD.

February 2-4—**Trauma Management—1987.** UCSD at Hotel Inter-Continental, San Diego. Monday-Wednesday. 20 hrs. Contact: UCSD.

February 22-27—**Emergency Medicine—1987.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sunday-Friday. Contact: UCD.

March 8-13—**8th Annual Mammoth Mountain Emergency Medicine Ski Conference.** UCI at Mammoth Lakes. Sunday-Friday. 20 hrs. Fee: $350. Contact: Medical Conferences, Inc, PO Box 52-B, Newport Beach 92662. (714) 650-4156.

March 16-20—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium II and Advanced Emergency Procedures Laboratory.** UCSD. Monday-Friday. 32 hrs. Fee: $325-440. Contact: UCSD.

April 11-18—**Infectious and Toxicologic Emergencies.** Scripps Memorial Hospital, Encinitas at Waiohai Resort and Poipu Beach Hotel, Kauai, HI. One week. 21 hrs. Fee: $375. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

INTERNAL MEDICINE

December 27-January 1—**Advances in Internal Medicine.** University of Washington at Kauai Sheraton, Kauai. Saturday-Thursday. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle 98195. (206) 543-1050.

January 14—**Urology Update.** LLU at LLU. Wednesday. 4 hrs. Fee: $60. Contact: LLU.

February 1-5—**Internal Medicine 1987: An Office Practice Review.** Sharp Memorial Hospital at Hotel Del Coronado, San Diego. Sunday-Thursday. 28 hrs. Fee: $395. Jackie Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

February 1-6—**Winter Urologic Forum.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sunday-Friday. 22 hrs. Fee: $370. Contact: UCD.

February 4-6—**Emerging Technology and Future Trends in Clinical Laboratory Molecular Analyses.** Scripps Clinic and Research Foundation at Vacation Village Resort, San Diego. Wednesday-Friday. 20 hrs. Contact: Bonny Mower, Dept of Academic Affairs, Scripps Clinic and Research Foundation, Box 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

February 8-13—**General Internal Medicine: Concepts and Controversies.** UCSF at Hyatt Lake Tahoe, Nevada. Sunday-Friday. Contact: UCSF

February 11-13—**20th Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday. 15 hrs. Contact: UCSF.

February 13-14—**5th Annual Infectious Disease.** UCD at Sacramento. Friday-Saturday. Contact: UCD.

March 11—**Rheumatology: Osteoarthritis and Nonsteroidal Drugs.** LLU. Wednesday. 4 hrs. Fee: $60. Contact: LLU.

March 30-April 1—**Federation of Western Societies of Neurological Science 24th Annual Meeting.** Monday-Wednesday at Hotel Del Coronado, Coronado. Contact: Patrick D. Lyden, MD, Dept of Neurosciences, UCSD Medical Center H-815A, 225 W Dickinson St, San Diego 92103. (619) 452-3940.

OB/GYN

December 4-6—**33rd Annual Scientific Meeting—Nebraska OB/GYN Society.** University of Nebraska at MGM Grand Hotel, Las Vegas, Nevada. Thursday-Saturday. 9 hrs. Fee: $200. Contact: Dennis Beavers, MD, 720 N 87th St, Omaha, NE 68114. (402) 390-1200.

December 4-7—**Current Issues in Perinatal Medicine.** UCI at Desert Princess Hotel, Palm Springs. Thursday-Sunday. Contact: UCI.

(Continued on Page 625)

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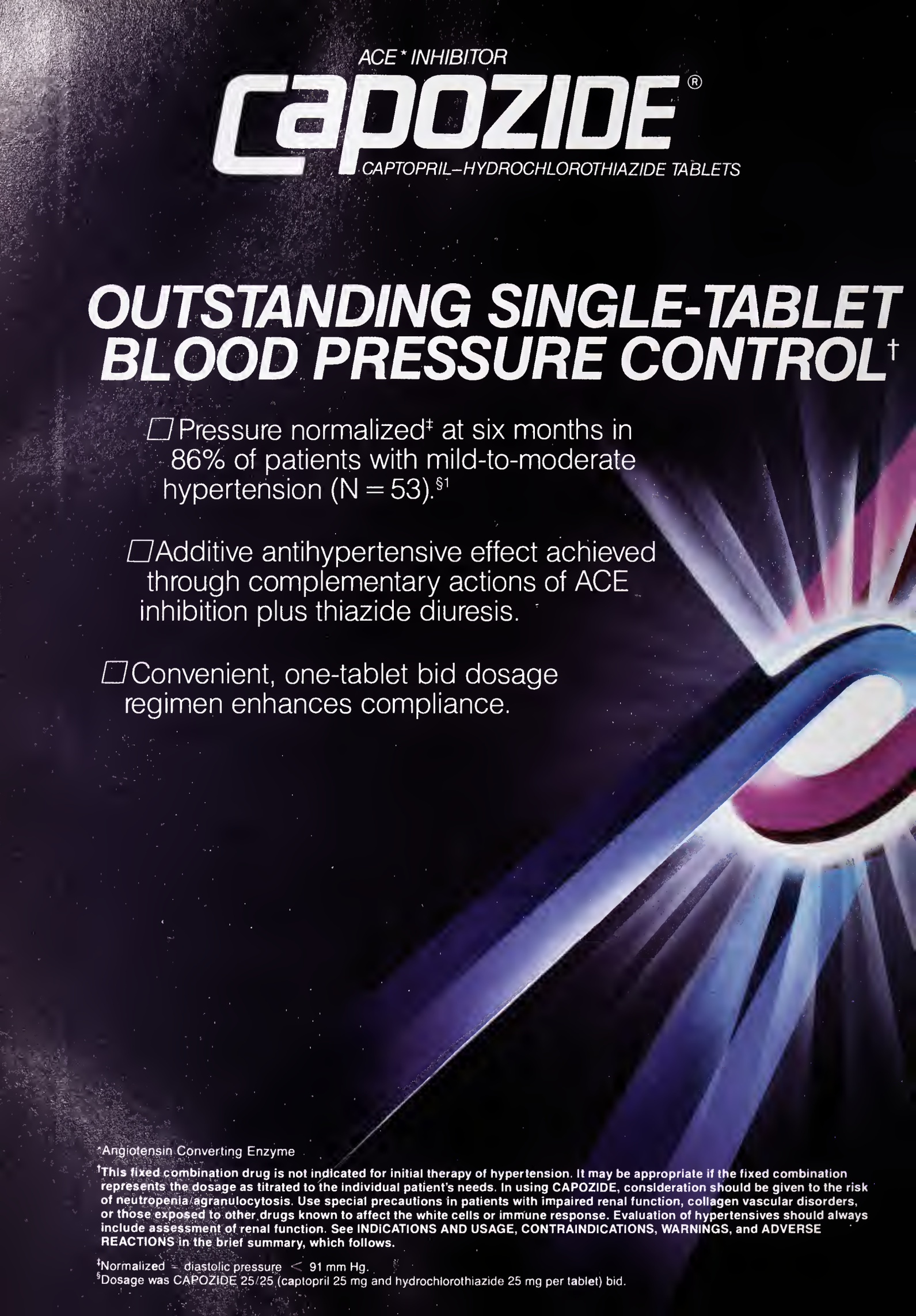

*Angiotensin Converting Enzyme

†**This fixed combination drug is not indicated for initial therapy of hypertension. It may be appropriate if the fixed combination represents the dosage as titrated to the individual patient's needs. In using CAPOZIDE, consideration should be given to the risk of neutropenia/agranulocytosis. Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. See INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, and ADVERSE REACTIONS in the brief summary, which follows.**

‡Normalized = diastolic pressure < 91 mm Hg.

§Dosage was CAPOZIDE 25/25 (captopril 25 mg and hydrochlorothiazide 25 mg per tablet) bid.

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References:
1. Lederle RM. Captopril and hydrochlorothiazide in the fixed combination multicenter trial. J Cardiovasc Pharmacol 7:S63–S69, 1985.
2. Weinberger MH: Influence of an angiotensin converting-enzyme inhibitor on diuretic-induced metabolic effects in hypertension. Hypertension 5(Suppl III):132S–138S, 1983.

Please see brief summary of prescribing information on adjacent page.

CAPOZIDE®
Captopril-Hydrochlorothiazide Tablets

INDICATIONS AND USAGE:—CAPOZIDE (Captopril-Hydrochlorothiazide Tablets) is indicated for the treatment of hypertension. **This fixed combination drug is not indicated for initial therapy of hypertension. If the fixed combination represents the dose titrated to the individual patient's needs, it may be more convenient than the separate components.** In using CAPOZIDE, consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOZIDE may be used for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, CAPOZIDE should be reserved for hypertensives who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to other drug combinations.

CONTRAINDICATION: Hydrochlorothiazide—Hydrochlorothiazide is contraindicated in patients with anuria and those who have previously demonstrated hypersensitivity to hydrochlorothiazide or other sulfonamide-derived drugs.

WARNINGS: Captopril—Neutropenia/Agranulocytosis—Neutropenia (<1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine <1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. Of reported cases, about half had serum creatinine ≥1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present. Neutropenia has appeared within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria—Total urinary proteins >1 g/day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy, patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

Hydrochlorothiazide—Use with caution in severe renal disease. May precipitate azotemia in patients with renal disease. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

PRECAUTIONS: General: Captopril—*Impaired Renal Function*—Some patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible (see DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]). *Surgery/Anesthesia*—If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Hydrochlorothiazide—Observe all patients for signs of fluid or electrolyte imbalance, particularly when the patient is vomiting excessively or receiving parenteral fluids. Warning signs include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and nausea and vomiting. Hypokalemia may develop when severe cirrhosis is present or without adequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of the heart to the toxic effects of digitalis. Because captopril reduces the production of aldosterone, concomitant therapy with captopril reduces the diuretic-induced hypokalemia. Fewer patients may require potassium supplements and/or foods with a high potassium content (see Drug Interactions, Agents Increasing Serum Potassium).

Any chloride deficit is generally mild and may not require specific treatment, exceptions include liver disease or renal disease. Dilutional hyponatremia may occur in edematous patients in hot weather; use water restriction, rather than salt administration except when the hyponatremia is life-threatening. In actual salt depletion, replacement is the therapy of choice. Hyperuricemia may occur or frank gout may be precipitated in certain patients. Latent diabetes mellitus may become manifest. Antihypertensive effects may be enhanced in the postsympathectomy patient. Progressive renal impairment, indicated by rising nonprotein nitrogen or blood urea nitrogen, requires a careful reappraisal of the necessity of therapy. Serum PBI levels may decrease. Calcium excretion is decreased. Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed during prolonged therapy.

Laboratory Tests—Serum and urine electrolyte levels should be regularly monitored (see WARNINGS, [Captopril and Hydrochlorothiazide], also PRECAUTIONS [General, Hydrochlorothiazide]).

Drug Interactions—Captopril—*Hypotension—Patients on Diuretic Therapy:* Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose. *Agents Having Vasodilator Activity:* In heart failure patients, vasodilators should be administered with caution. *Agents Causing Renin Release:* Captopril's effect will be augmented by antihypertensive agents that cause renin release. *Agents Affecting Sympathetic Activity:* The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution. *Agents Increasing Serum Potassium:* Give potassium sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution. *Inhibitors Of Endogenous Prostaglandin Synthesis:* Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Hydrochlorothiazide—When administered concurrently the following drugs may interact with thiazide diuretics: *Alcohol, barbiturates, or narcotics*—potentiation of orthostatic hypotension may occur. *Antidiabetic drugs (oral agents and insulin)*—Hyperglycemia induced by thiazides may require dosage adjustment of the antidiabetic drug. *Other antihypertensive drugs*—additive effect or potentiation. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. *Corticosteroids, ACTH*—intensified electrolyte depletion, particularly hypokalemia. *Preanesthetic and anesthetic agents*—effects of preanesthetic and anesthetic agents may be potentiated; adjust dosage of these agents accordingly. *Pressor amines (e.g., norepinephrine)*—possible decreased response to pressor amines but not sufficient to preclude their use. *Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)*—possible increased responsiveness to the muscle relaxant. *Lithium*—should not generally be given with diuretics; diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with CAPOZIDE.

Drug/Laboratory Test Interactions—Captopril—may cause a false-positive urine test for acetone.

Hydrochlorothiazide—Discontinue thiazides before carrying out tests for parathyroid function (see PRECAUTIONS [General, Hydrochlorothiazide]).

Carcinogenesis, Mutagenesis and Impairment of Fertility—Captopril—Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Hydrochlorothiazide—Long-term studies in animals have not been performed to evaluate carcinogenic potential, mutagenesis, or whether this drug affects fertility in males or females.

Pregnancy: Category C—Captopril—There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Hydrochlorothiazide—Studies in pregnant rats using captopril and hydrochlorothiazide individually and in combination, each agent in doses up to 1350 mg/kg, failed to show evidence of embryotoxicity, fetotoxicity, or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CAPOZIDE should be used during pregnancy, or in patients likely to become pregnant, only if the potential benefit justifies the potential risk to the fetus.

Pregnancy—Nonteratogenic Effects—Hydrochlorothiazide—Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the benefit be weighed against possible hazards to the fetus. Hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other reported reactions.

Nursing Mothers: Both captopril and hydrochlorothiazide are excreted in human milk. A potential exists for serious adverse reactions in nursing infants from both drugs, therefore, decision whether to discontinue nursing or to discontinue therapy should take into account the importance of CAPOZIDE (Captopril-Hydrochlorothiazide Tablets) to the mother.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. CAPOZIDE should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Captopril—Reported incidences are based on clinical trials involving approximately 7000 patients. *Renal*—About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients. *Hematologic*—Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported. *Dermatologic*—Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients. *Cardiovascular*—Hypotension may occur, see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients. *Dysgeusia*—About 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Hydrochlorothiazide—*Gastrointestinal System*—anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, and sialadenitis. *Central Nervous System*—dizziness, vertigo, paresthesias, headache, and xanthopsia. *Hematologic*—leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, and hemolytic anemia. *Cardiovascular*—orthostatic hypotension. *Hypersensitivity*—purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis; cutaneous vasculitis), fever, respiratory distress including pneumonitis, and anaphylactic reactions. *Other*—hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, and transient blurred vision. Whenever adverse reactions are moderate or severe, reduce or withdraw therapy.

Altered Laboratory Findings: Elevations of liver enzymes have been noted in a few patients but no causal relationship to captopril use has been established. Rare cases of cholestatic jaundice and of hepatocellular injury with or without secondary cholestasis have been reported in association with captopril administration. A transient elevation of BUN and serum creatinine may occur, especially in patients who are volume-depleted or who have renovascular hypertension. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in the serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Captopril—Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

Hydrochlorothiazide—In addition to diuresis, overdosage of thiazides may produce varying degrees of lethargy which may progress to coma within a few hours, with minimal respiratory and cardiovascular depression and without evidence of serum electrolyte changes or dehydration. The mechanism of thiazide-induced CNS depression is unknown. Gastrointestinal irritation and hypermotility may occur. Transitory increase in BUN has been reported, and serum electrolyte changes may occur, especially in patients with impaired renal function. In addition to gastric lavage and supportive therapy for stupor or coma, symptomatic treatment of gastrointestinal effects may be needed. Degree of removal by hemodialysis has not been clearly established. Measures to maintain hydration, electrolyte balance, respiration, and cardiovascular and renal function should be instituted.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED (SEE INDICATIONS AND USAGE). CAPOZIDE (Captopril-Hydrochlorothiazide Tablets) should be taken one hour before meals. CAPOZIDE may be dosed bid or tid. Because captopril and hydrochlorothiazide are excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOZIDE (Captopril-Hydrochlorothiazide Tablets).

Available in tablets of 25 mg captopril combined with 15 mg hydrochlorothiazide, 25 mg captopril combined with 25 mg hydrochlorothiazide, 50 mg captopril combined with 15 mg hydrochlorothiazide, and 50 mg captopril combined with 25 mg hydrochlorothiazide in bottles of 100.

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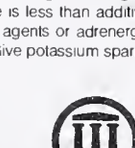

INNOVATORS IN CARDIOVASCULAR MEDICINE

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(Continued from Page 620)

December 10—**Lifestyles and Perinatal Outcome.** Perinatal Advisory Council of Los Angeles Communities at Broadway Plaza Hyatt Regency, Los Angeles. Wednesday. 7 hrs. Fee: $75. Contact: Marilyn Cejka Steinberg, PAC, 3250 Wilshire Blvd, Ste 206, Los Angeles 90010. (213) 380-1790.

December 11-13—**Advanced Ultrasound.** American College of OB/GYN at Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. 16 hrs. Contact: ACOG, 600 Maryland Ave SW, Ste 300 East, Washington, DC 20024-2588. (202) 863-2542.

January 12-16—**OB/GYN Review II.** USC at Pasadena Hilton Hotel. Monday-Friday. 35.75 hrs. Fee: $545. Contact: USC.

January 14-17—**GYN Review.** USC at Pasadena Hilton Hotel. Wednesday-Saturday. 28.5 hrs. Fee: $430. Contact: USC.

January 16-18—**Gynecology Update for the Primary Care Physician.** UCSD at Vacation Village Resort, San Diego. Friday-Sunday. 15 hrs. Fee: $275. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 17—**OB/GYN Pathology II.** USC at Pasadena Hilton Hotel. Saturday. 6.25 hrs. Fee: $105. Contact: USC.

February 1-5—**OB/GYN Update—1987.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sunday-Thursday. Contact: UCD.

February 7-13—**Perinatal Medicine.** USC at Royal Lahaina Hotel, Hawaii. Saturday-Friday. 23 hrs. Fee: $525. Contact: USC.

February 8-12—**15th Obstetric Anesthesia Conference.** Ohio State University Hospital at Sheraton Waikiki Hotel, Hawaii. Sunday-Thursday. Contact: OSU Hospital, Dept of Anesthesiology, 410 W 10th Ave, Columbus, OH 43210. (614) 421-8487.

February 21—**Infertility Update IV.** Scripps Clinic and Research Foundation, La Jolla. Saturday. 6 hrs. Contact: Bonny Mower, Dept of Academic Affairs, Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

March 25-28—**GYN Urology.** UCI at Hilton Riviera, Palm Springs. Wednesday-Saturday. Contact: UCI.

April 2-4—**Fetal Diagnosis and Treatment.** UCSD. Thursday-Saturday. Contact: UCSD.

April 30-May 2—**12th Annual Symposium: Care of the Sick Newborn.** UCI. Thursday-Saturday. Contact: UCI.

OPHTHALMOLOGY

December 11-12—**An Update in Neuro-Ophthalmology.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Friday. Contact: UCSF.

PATHOLOGY

January 17—**OB/GYN Pathology II.** USC at Pasadena Hilton Hotel. Saturday. 6.25 hrs. Fee: $105.

PEDIATRICS

November 21-24—**8th Annual American Academy of Pediatrics Las Vegas Seminars: Pediatric Update.** American Academy of Pediatrics at Caesars Palace, Las Vegas. Friday-Monday. 15.5 hrs. Fee: $295. Contact: AAP, PO Box 2134, Inglewood 90305. (213) 757-1198.

December 6—**5th Annual Binational Workshop: Border Health Problems—Pediatrics Infectious Disease.** Children's Hospital, San Diego. Saturday. 5 hrs. Contact: Ann Albrecht, Children's Hospital, 8001 Frost St, San Deigo 92123. (619) 576-1700

January 19-21—**Pediatrics for the Primary Care Physician.** UCSD at Vacation Village Resort, San Diego. Monday-Wednesday. 16 hrs. Fee: $275. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 24-31—**Pediatric Emergencies.** Scripps Memorial Hospital, Encinitas at Kona Surf Resort, Hawaii. One week. 21 hrs. Fee: $375. Contact: Edith Bookstein/AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

January 30-February 1—**25th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Marriott Hotel. Friday-Sunday. 15 hrs. Fee: $175. Contact: Wayne Herbert, MD, Children's Hospital of Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

February 3-8—**16th Annual Pediatric Postgraduate Course: Pediatric Update 1987.** Schneider Children's Hospital of Long Island Jewish Medical Center, Rancho Las Palmas, Palm Springs. Tuesday-Sunday. Contact: Ann J. Boehme, Schneider Children's Hospital of Long Island Jewish Medical Center, New Hyde Park, NY 11042. (718) 470-8650.

February 5-7—**Current Concepts in Pediatric Medicine.** American Academy of Pediatrics at Holiday Inn Embarcadero, San Diego. Thursday-Saturday. 16 hrs. Fee: $330. Contact: Neal A. Baker, AAP, Division of Continuing Education, PO Box 927, Elk Grove Village, IL 60007. (800) 433-9016, or in Illinois (800) 421-0589.

February 16-18—**Pediatrics Update 1987.** Continuing Medical Education Associates at Hyatt Islandia Hotel, San Diego. Monday-Wednesday. 18 hrs. Fee: $275. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

March 5-7—**Advances in Pediatrics II.** American Academy of Pediatrics at Kauai, Hawaii. Thursday-

Saturday. 16 hrs. Fee: $330. Contact: Neal A. Baker, Div of Continuing Education, AAP, PO Box 927, Elk Grove Village, IL 60007. (800) 433-9016, or in Illinois (800) 421-0589.

April 2-4—**20th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. Contact: UCSF.

April 8—**Pediatrics: Genetics.** LLU. Wednesday. 4 hrs. Fee: $60. Contact: LLU.

PSYCHIATRY

December 28-January 3—**Psychiatry and the Practicing Physician—"New Year '87—Maui."** Hawaii Medical Association at Royal Lahaina Resort, Kaanapali Beach, Maui. Sunday-Saturday. 16.5 hrs. Fee: $385. Contact: Joe Harrison, MD, Symposium Maui, Inc, PO Box 10185, Lahaina, HI 96761. (808) 879-8182.

January 25-30—**13th Annual Midwinter Program for Psychiatrists: Special Focus on Adolescent Psychiatry.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sunday-Friday. 25 hrs. Fee: $355-415. Contact: UCD.

RADIOLOGY

November 15-16—**Magnetic Resonance Imaging.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Saturday-Sunday. 10 hrs. Fee: $200. Contact: LARS-MRI, PO Box 91215, Los Angeles 90009-1215. (213) 642-0921.

December 8-11—**Chest Imaging.** UCSD at Hotel del Coronado, Coronado. Monday-Thursday. 24 hrs. Contact: UCSD.

December 11-13—**Advanced Ultrasound.** American College of OB/GYN at Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. 16 hrs. Contact: ACOG, 600 Maryland Ave SW, Ste 300 East, Washington, DC 20024-2588. (202) 863-2542.

January 9-13—**Advance Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Hotel, Laguna Niguel. Friday-Tuesday. 20 hrs. Contact: Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 12-16—**Neurodiagnostic Imaging: MRI.** UCSF at Hyatt Regency Hotel, San Francisco. Monday-Friday. Contact: UCSF.

January 13-16—**Chest Radiology—1987.** UCSD at Hotel Del Coronado, Coronado. Tuesday-Friday. 22 hrs. Contact: Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 22-24—**Practical Approach to Duplex Imaging.** UCSD at San Diego Hilton Hotel. Thursday-Saturday. Contact: UCSD.

January 30-February 1—**10th Annual Evoked Potential and Electrodiagnostic Workshop.** UCI. Friday-Sunday. 20 hrs. Contact: UCI.

January 30-February 1—**39th Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. 21 hrs. Fee: $350. Contact: Diane L. Johnson, Los Angeles Radiological Society, 5200 Century Blvd, Ste 920, Los Angeles 90045. (213) 642-0921.

February 2-6—**Radiology: Imaging and Intervention.** UCSD at Hotel Inter-Continental, San Diego. Monday-Friday. Contact: R. Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

February 3-7—**13th Annual Midwinter Radiological Post Conference Seminar.** Los Angeles Radiological Society at Hyatt Regency, Kaanapali, Maui, Hawaii. Tuesday-Saturday. 18 hrs. Fee: $375. Contact: LARS-MWRC, PO BOX 91215, Los Angeles 90009-1215. (213) 642-0921.

February 11—**Interventional Radiology.** LLU at LLU. Wednesday. 4 hrs. Fee: $60. Contact: LLU.

February 21-28—**Radiology for Emergency and Primary Care Physicians.** Scripps Memorial Hospital, Encinitas at Royal Lahaina Resort, Maui, Hawaii. One week. 21 hrs. Fee: $375. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

March 2-5—**Neuroradiology Update.** UCSD at Hotel Del Coronado, Coronado. Monday-Thursday. Contact: Mary J. Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

March 3-6—**Magnetic Resonance Imaging.** UCSD at Hotel Del Coronado, Coronado. Tuesday-Friday. Contact: Mary J. Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

March 7-8—**Breast Imaging Update.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday. Contact: UCSF.

March 9-13—**30th Annual Diagnostic Radiology Postgraduate Course.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. Contact: UCSF.

March 14-15—**Contemporary Trends in Diagnostic Nuclear Medicine.** UCSF at Hyatt Regency Hotel, San Francisco. Saturday-Sunday. Contact: UCSF.

March 16-21—**Diagnostic Imaging—1987.** UCSF at Waiohai Hotel, Kauai, Hawaii. Monday-Saturday. Contact: UCSF.

(Continued on Page 633)

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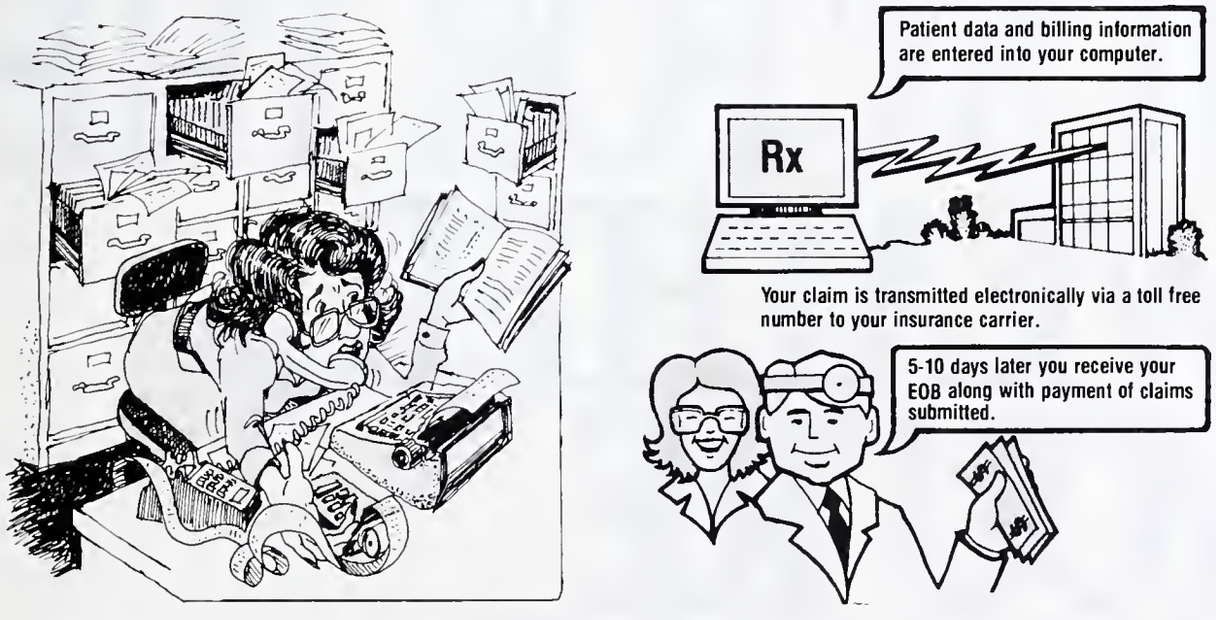

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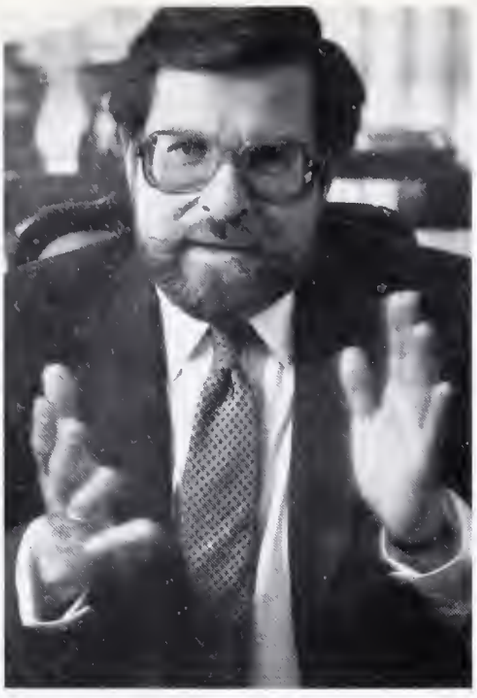
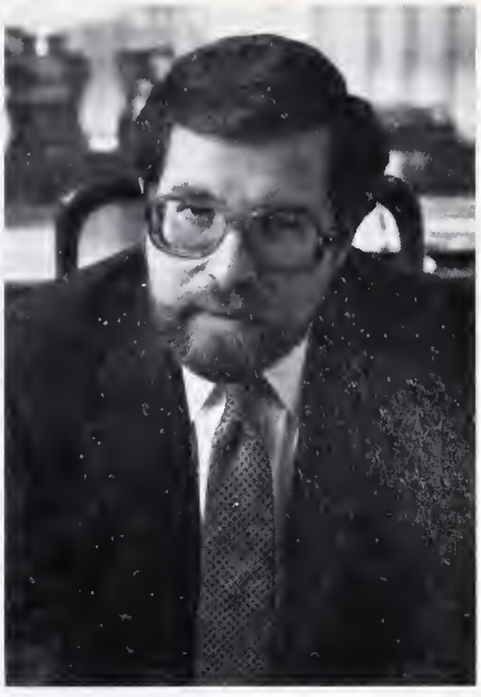


"Already, we've been talking to a lot of physicians and hospitals face-to-face, getting their input on how we can become a more service-oriented organization. Their biggest concern is that our claim payments are on the slow side. And they're right. But I can honestly say improvements with that are already in the works. As far as individual and group plans go, they seem to like what we're doing. They understand that as hard as it is today to keep costs down, no one is doing a better job."



"We're in this together. We can't function without the hospitals and physicians, and vice-versa, they can't operate without us. And it's true, times are tough right now. But recently I was elected to the Board of Directors of the Southern California Hospital Association. So there's an exchange going on of thoughts and ideas. And that's encouraging. It can only make things better. After all, our goal is to make it as easy as possible for hospitals. To always be there when they need us. And I think we're heading in the right direction."

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†CAPOTEN may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. See INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

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Comparison of Adverse Effects for CAPOTEN (≤ 100 mg) versus Placebo in Hypertensive Patients with Normal Renal Function (N = 1,622)‡[2]

ADVERSE EFFECT	CAPOTEN (N = 1,174) (% affected)	Placebo (N = 448) (% affected)
Headache	5.2	6.9
Rash	3.7	2.5
Dizziness	3.5	2.0
Nausea	3.2	2.0
Fatigue	3.1	2.0
Taste alteration	1.5	1.1
Gastrointestinal	1.4	0.7
Diarrhea	1.1	1.1

‡None of the differences between captopril and placebo was statistically significant. For the most part, adverse effects were mild and transient and usually did not require discontinuation of therapy. Only 5.5% of the patients in this data base discontinued because of an adverse effect. Data include adverse effects for CAPOTEN with an incidence greater than 1%.

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INDICATIONS: Hypertension – CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia ($<1000/mm^3$) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine < 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count $<1000/mm^3$) withdraw captopril and closely follow the patient's course.

Proteinuria – Total urinary proteins >1 g/day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy, patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension – Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function,* Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction.

Surgery/Anesthesia – If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C – There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic – Neutropenia/agranulocytosis have occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients – reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur, see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia – About 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg also available in bottles of 1000), and in UNIMATIC® single dose packs of 100 tablets. (J3-658D)

References:

1. PDS Alpha, *National Prescription Report,* Pharmaceutical Data Services, Subsidiary of McKesson Corporation.
2. Data on file, Squibb Institute for Medical Research.

SQUIBB

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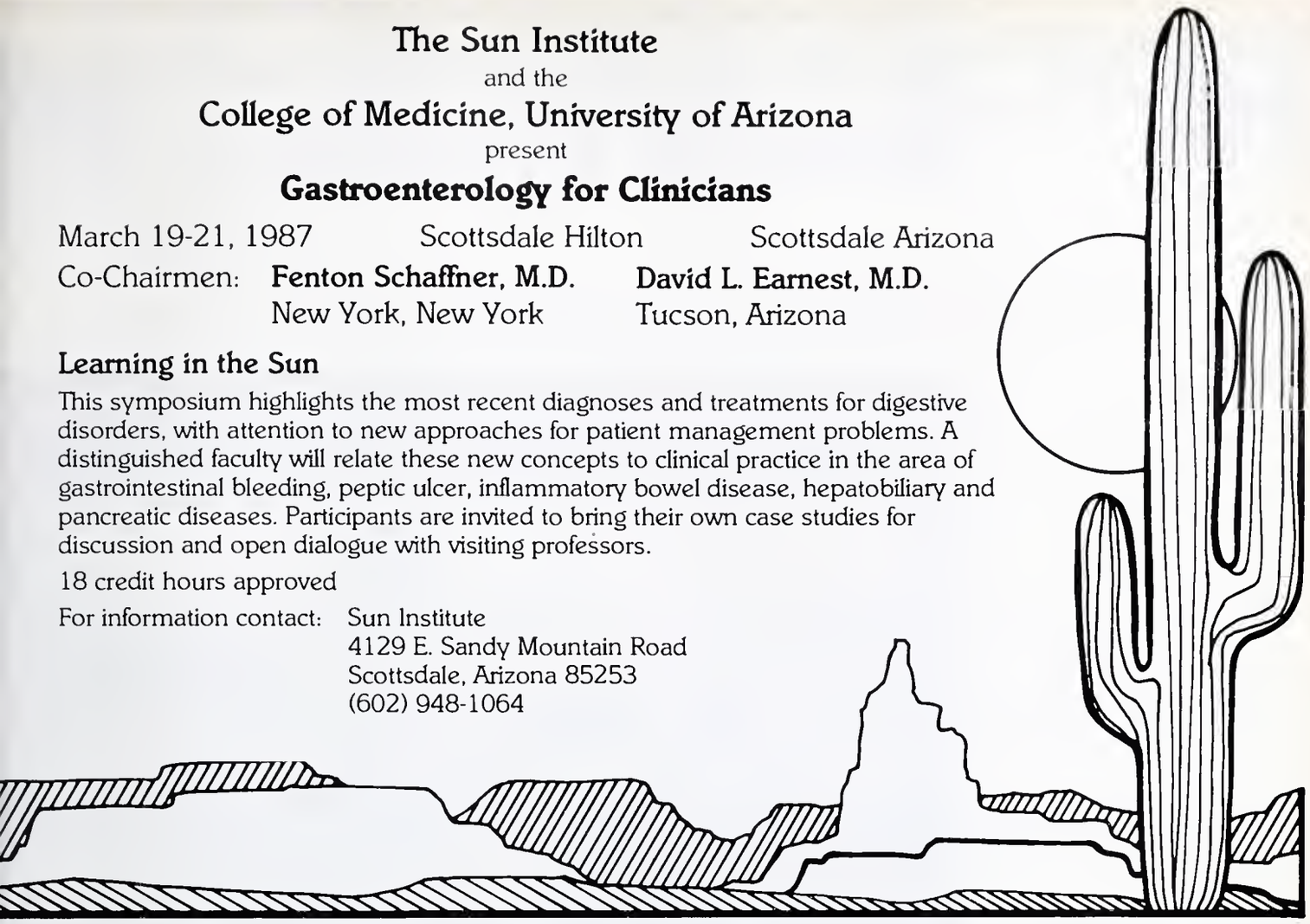

CONTINUING MEDICAL EDUCATION

(Continued from Page 626)

April 9-11—**Thoracic Imaging—1987.** UCSF at Hyatt Regency, Monterey. Thursday-Saturday. Contact: UCSF.

April 10-12—**OB/GYN and Abdominal Sonography: Update 1987.** UCSF at Hyatt Regency on Union Square, San Francisco. Friday-Sunday. Contact: UCSF.

April 19-25—**7th Annual San Diego Residents' Radiology Review Course.** UCSD at Town and Country Hotel, San Diego. Sunday-Saturday. Contact: UCSD.

SPORTS MEDICINE

November 25-28—**Sports Medicine.** American College of Sports Medicine and Children's Hospital Medical Center, Oakland at Inter-Continental Hotel, Maui. Tuesday-Friday. 25 hrs. Fee: $300. Contact: Stuart Zeman, MD, Course Chairman, 2999 Regent St, Ste 203, Berkeley 94705. (415) 540-8686.

December 10—**Orthopedic Surgery: Sports Injuries.** LLU at LLU. Wednesday. 6 hrs. Fee: $60. Contact: LLU.

January 18-23—**Sports Medicine—1987.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sunday-Friday. Contact: UCD.

SURGERY

December 4-7—**2nd Annual Fracture Management Symposium.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Thursday-Sunday. 18 hrs. Fee: $475. Contact: UCD.

December 7-19—**Temporal Bone Surgical Dissection and Cochlear Implant.** House Ear Institute. Sunday-Friday. 100 hrs. Fee: $1,700. Contact: Antonio De La Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

January 19-21—**American Society for Surgery of the Hand's 1st Winter Meeting.** Pacific Medical Center, San Francisco. Monday-Wednesday. Contact: American Society for Surgery of the Hand, 3025 S Parker Rd, Ste 65, Aurora, CO 80014.

January 19-23—**10th Annual Postgraduate Assembly in Surgery.** UCSD at US Grant Hotel, San Diego. Monday-Friday. 26.5 hrs. Fee: $275. Contact: UCSD.

January 22-24—**9th Annual Surgical Postgraduate**

(Continued on Page 636)

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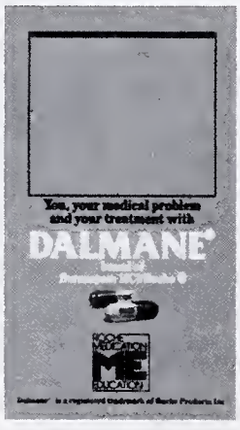

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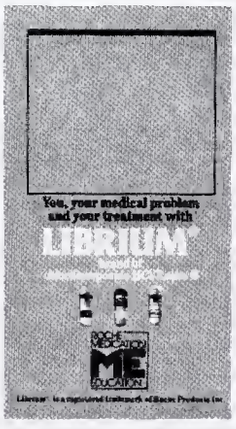

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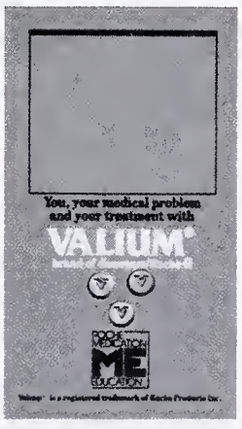

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(Continued from Page 633)

Course. UCD at Capitol Plaza Holiday Inn, Sacramento. Thursday-Saturday. 14 hrs. Contact: UCD.

January 25-31—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Sunday-Saturday. 62 hrs. Fee: $950. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

February 17-19—**Maxillofacial Trauma.** USC. Tuesday-Thursday. 16 hrs. Fee: $500. Contact: USC.

February 22-28—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Sunday-Saturday. 62 hrs. Fee: $950. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

March 6-8—**Cruciate Ligament Surgery: Principles and Practice.** Scripps Clinic and Research Foundation at Marriott Hotel, La Jolla. Friday-Sunday. 23 hrs. Contact: Bonny A. Mower, Dept of Academic Affairs, Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

March 8-14—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Sunday-Saturday. 62 hrs. Fee: $950. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

March 18-20—**Preoperative Evaluation of the Surgical Patient.** UCSF at Holiday Inn Union Square, San Francisco. Wednesday-Friday. 16 hrs. Fee: $325. Contact: UCSF.

March 30-April 10—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Monday-Friday. 100 hrs. Fee: $1,750. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

April 11-18—**Surgery.** University of Washington at Royal Lahaina Hotel, Maui, Hawaii. One week. Contact: University of Washington School of Medicine, Div of CME, Sc-50, Seattle, WA 98195. (206) 543-1050.

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November 17-20—**11th Annual Family Practice Update.** LLU at LLU. Monday-Thursday. 28 hrs. Fee: $350.

November 21—**Orthopedic Symposium.** Kaiser Permanente Medical Group at Marina Beach Hotel, Marina Del Rey. Friday. 7 hrs. Fee: $100. Contact: Judy Harrison, Dept of Clinical Services, Southern California Permanente Medical Group, 393 E Walnut St, Pasadena 91188. (818) 405-5000.

November 22—**Alzheimer's Disease—An Overview.** UCI at UCI. Saturday. 5.5 hrs. Contact: UCI.

November 29-December 6—**Behavioral Medicine Topics That Make Sense for Your Practice—Hawaiian Island Cruise Adventure.** University of Arizona at Hawaii. One week. 24 hrs. Contact: Epic Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

December 5-6—**2nd Annual Clinical Nutrition Update for the Practicing Physician.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 12 hrs. Fee: $165. Contact: UCD.

December 5-6—**Psychosocial Intervention in Cancer and AIDS.** University of Illinois College of Medicine at La Jolla Marriott Hotel, La Jolla. Friday-Saturday. 13 hrs. Fee: $150. Contact: Carle Medical Communications, 510 West Main, Urbana, IL 61801. (217) 384-4838.

December 5-7—**3rd Annual Common Office Problems for the Primary Care Physician.** Cypress Foundation at Hyatt Regency, Monterey. Friday-Sunday. 12 hrs. Contact: Cypress Foundation, PO Box 80308, Salinas 93912. (408) 455-1833.

December 9—**Acquired Immune Deficiency Syndrome: Update 1986.** Daniel Freeman Memorial Hospital, Inglewood. Tuesday. 6 hrs. Contact: Daniel Freeman Memorial Hospital, (213) 674-7050, ext 3427.

December 11-12—**AIDS and the Nervous System.** UCSF at St Francis Hotel, San Francisco. Thursday-Friday. 11 hrs. Contact: UCSF.

January 12-16—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD at San Diego Hilton Hotel. Monday-Friday. 32 hrs. Fee: $325-400. Contact: UCSD.

January 16-17—**Cardiology for the Non-Cardiologist.** UCI at Long Beach. Friday-Saturday. Contact: UCI.

January 18-20—**Physical Examination of the Child Sexual Molest Victim: The State of the Art.** Children's Hospital, San Diego at Hanalei Hotel, San Diego. Sunday-Tuesday. 15.5 hrs. Fee: $200. Contact: Ann Albrecht, Children's Hospital, 8001 Frost St, San Diego 92123. (619) 576-1700.

January 18-23—**Nevada Academy of Family Physicians Winter Assembly: Living Healthier Longer.** Caesar's Tahoe Hotel and Casino, Nevada. Sunday-Friday. 34 hrs. Fee: $400. Contact: Dottie Batchelor, NAFP, PO Box 7471, Reno, NV 89510-7471. (702) 826-5100.

January 19-21—**Pediatrics for the Primary Care Physician.** UCSD at Vacation Village Resort, San Diego. Monday-Wednesday. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 20-24—**Intensive Course in Geriatric Medi-**

(Continued on Page 718)

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This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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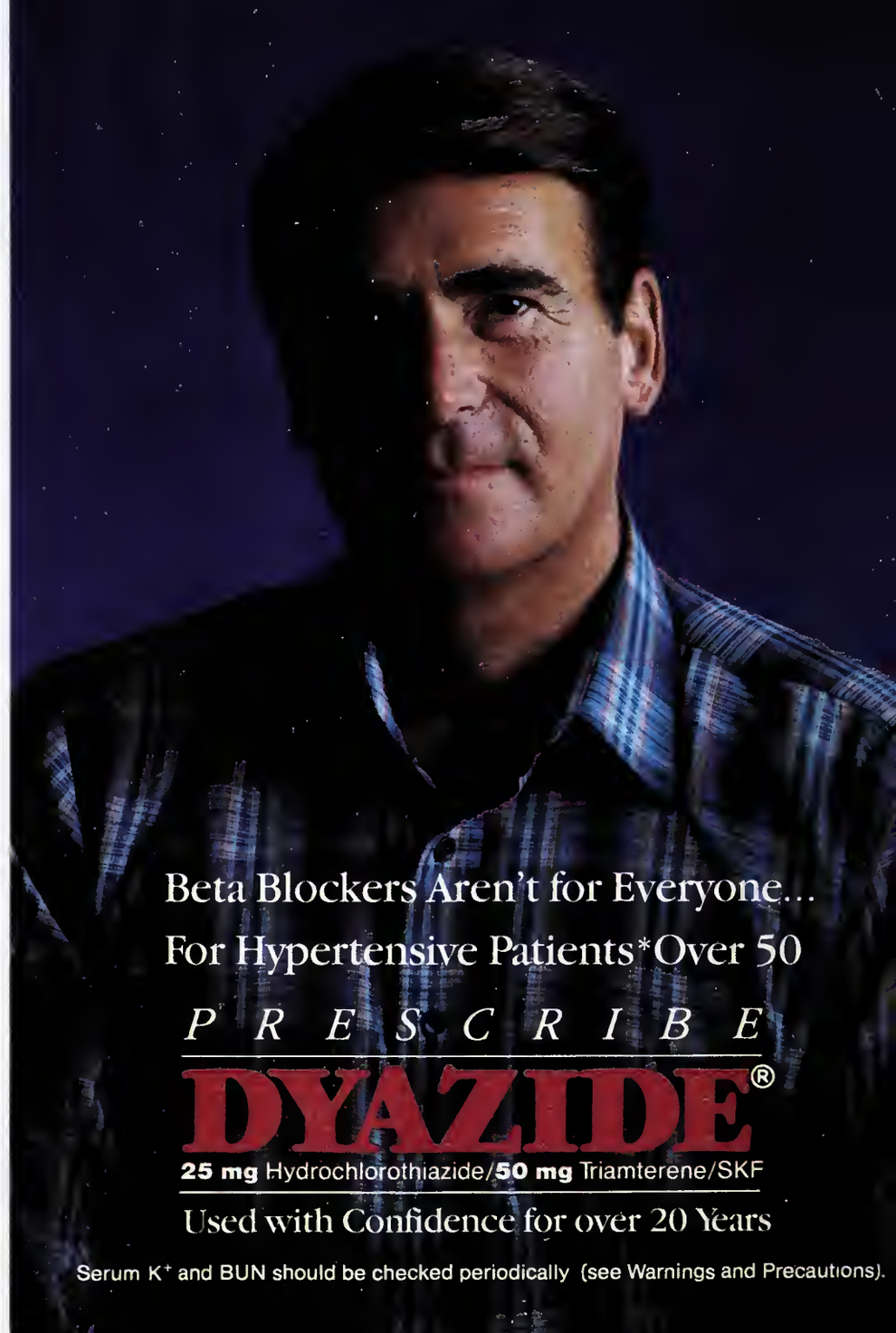

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Sudden Death Prediction By Programmed Electrical Stimulation Following Myocardial Infarction

JACK KRON, MD; CURTIS K. LI, MD; EDWARD MURPHY, MD; DAVID BROUDY, MD; CYNTHIA MORRIS, PhD; KAREN GRIFFITH, RN, MN, *and* JOHN H. McANULTY, MD, *Portland*

To determine prospectively whether electrophysiologic testing is prognostically useful following a myocardial infarction, 38 patients were studied. Ventricular tachycardia was induced in 32 of 38 (84%) patients (sustained in 12) and was significantly increased with the use of three or four extrastimuli. In 17 months' mean follow-up, 4 patients died suddenly or survived an episode of sustained ventricular tachycardia. Programmed ventricular stimulation was a sensitive but not a specific predictor of these events with an overall 24% predictive accuracy. The use of one or two extrastimuli substantially improved specificity but was insensitive in predicting sudden death or ventricular tachycardia. Programmed ventricular stimulation soon after uncomplicated myocardial infarction was not a useful prognostic indicator for sudden death or subsequent ventricular tachycardia.

(Kron J, Li CK, Murphy E, et al: Sudden death prediction by programmed electrical stimulation following myocardial infarction. West J Med 1986 Nov; 145:639-644)

One tenth of survivors of a myocardial infarction will die suddenly within a year.[1] Ventricular ectopy,[2] reduced left ventricular function,[3] bundle branch block[4] and exercise testing results[5] have been identified as potential markers for a subsequent early sudden death. As most sudden deaths are due to ventricular fibrillation,[6] attempts to look for markers for potentially treatable ventricular tachyarrhythmias seem appropriate. Several authors[7-9] have been encouraged about the prognostic value of programmed ventricular stimulation in survivors of myocardial infarctions. Others, however, have found programmed ventricular stimulation not to be predictive of subsequent sudden death.[10-12]

In a prospective study we have evaluated the role of programmed ventricular stimulation as a prognostic procedure in patients receiving β-blockers following discharge from a coronary care unit after a myocardial infarction.

Patients and Methods

Patient Entry Criteria

Patients in the coronary care unit at the Oregon Health Sciences University Hospital and the Portland Veterans Administration Medical Center were approached if they met the criteria for an acute myocardial infarction. Approval was obtained from the Oregon Health Sciences University Human Use Committee and informed consent was obtained from each participant. A myocardial infarction was diagnosed when the clinical history was compatible, when there was a rise in a serum creatine kinase level to at least 175 IU associated with a positive MB fraction and if there were serial ST-T-wave changes (a non-Q-wave infarction) or significant Q waves (0.04 seconds in duration; a Q-wave infarction).

All patients were monitored in the coronary care unit for 24 to 72 hours. Left ventricular cineangiography and coronary angiography or gated radionuclide angiocardiography (or all three) was done only for clinical purposes. When available, an ejection fraction was determined in these patients by the area length method[13] or by multiple-gated imaging.[14]

A β-blockade regimen was started (unless specifically contraindicated), and seven to ten days following hospital admission, each patient was asked to undergo an investigational intracardiac electrophysiologic study.

Exclusion criteria included severe heart failure, thrombo-

From the Department of Medicine, Division of Cardiology, Oregon Health Sciences University, Portland.

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Reprint requests to Jack Kron, MD, Division of Cardiology, Oregon Health Sciences University, Portland OR 97201.

embolic events, refractory recurrent chest pain and ventricular tachycardia or fibrillation that occurred following discharge from the coronary care unit.

Electrophysiologic Studies

Under fluoroscopic guidance, two standard electrode catheters were positioned along the lateral right atrial wall and the His bundle recording site. A polyethylene catheter was inserted percutaneously in the brachial artery for pressure recording. Patients were studied in a fasting nonpremedicated state using 0.5% lidocaine for local anesthesia. The use of β-blockers was continued throughout the study.

After baseline interval recording and an atrial stimulation study, the ventricular stimulation protocol was carried out. Ventricular burst pacing of 16 beats was done, starting at a rate of 100 beats per minute and increasing by 20 beat-per-minute increments until a ventricular rate of 200 beats per minute (or angina) was achieved.

The ventricular extrastimulus technique followed, using single through quadruple extrastimuli during sinus rhythm and then with ventricular pacing at a cycle length of 545 ms. The ventricular beat was introduced 400 ms following the last QRS complex and then decreased by 20-ms intervals until the effective refractory period of the ventricle was achieved. The first extrastimulus was left 50 ms above the effective refractory period and a second extrastimulus was introduced at a coupling interval of 310 ms beyond the first extrastimulus. The second extrastimulus was decreased in 20-ms decrements, and the technique was then carried out with a third and fourth extrastimulus. The ventricular pacing catheter was repositioned in the ventricle to test a second site and the stimulation protocol was repeated.

The study was terminated with completion of this protocol, with creation of a sustained arrhythmia or if nonsustained ventricular tachycardia was induced with the quadruple extrastimulus technique. This last criterion was included after it was found that 53% of the first 15 patients studied had sustained rhythms induced with the fourth extrastimulus and after discussion with an advisory committee.

All stimulation protocols were done with a programmable stimulator (manufactured by Bloom Associates, Narberth, Pennsylvania) using a rectangular pulse of 2 ms in duration and 5 mA in amplitude.

Definitions of Responses to Ventricular Stimulation

Repetitive ventricular response. This term is used when two to four ventricular beats occur in response to the last ventricular pacing stimulus.[15]

Ventricular tachycardia. (1) Nonsustained ventricular tachycardia is five or more ventricular beats in response to the last ventricular pacing stimulus not requiring therapeutic intervention, and (2) sustained ventricular tachycardia is ventricular tachycardia or fibrillation lasting longer than 30 seconds or requiring therapeutic intervention.

Data Analysis

Data were analyzed using χ^2 and sensitivity and specificity analysis. Survival was determined by Kaplan-Meier survival curves, and the difference between the curves was determined by Breslow and Mantel-Cox statistics.

Results

Study Patients

From July 1, 1982, through July 1, 1983, 110 patients were identified as eligible for this study. From this, 38 (35%) consented to participate (Table 1). The age range in the 35 men and 3 women was 34 to 74 years, and 11 had an anterior wall infarction, 12 an inferior wall infarction, 1 a lateral infarction, 13 a nontransmural infarction and in 1 the site was not determined because of left bundle branch block. The peak creatine kinase level ranged from 248 to 5,040 IU (mean 1,353 IU). The postinfarction ejection fraction using either angiographic or radionuclide techniques (N = 31) ranged from 0.24 to 0.71 (mean of 0.46). All except two patients had a segmental wall motion abnormality.

In all, 28 patients were on a β-blockade regimen at the time of the study, 10 were not (4 had significant congestive heart failure, 4 had bradycardia, 1 had reactive airway disease and 1 because of private physician preference). The heart rate averaged 65 beats per minute in the 28 patients who were receiving β-blockers and 74 beats per minute in the 10 who were not on the therapy. Three were taking antiarrhythmic agents at the time of the study—one phenytoin because of a seizure disorder, and one each quinidine and procainamide for treatment of supraventricular arrhythmias.

Incidence of Rhythms Induced

Repetitive ventricular responses were induced in all 38 patients. Ventricular tachycardia was induced in 32 of 38 patients (84%) (sustained in 12, of whom 6 had a monomorphic rhythm). The induction of sustained ventricular tachycardia possibly could have been higher with quadruple extrastimuli but, as defined in the methods, the protocol was designed to stop the study when nonsustained ventricular tachycardia was induced.

Ventricular tachycardia was not induced with a single extrastimulus in any patient, was brought out by double extrastimuli in only two patients and required triple or quadruple extrastimuli in the majority of patients (Figure 1).

A repetitive ventricular response induced with single or double extrastimuli did not define those in whom either nonsustained or sustained ventricular tachycardia was subsequently induced ($P > .05$).

Effect of Second Ventricular Pacing Site

The limitations of our protocol did not allow direct comparison of arrhythmia inducibility at the first site versus a second site. Once ventricular tachycardia was induced, the protocol was terminated and, if this occurred at the first site, a second was not tested. A second right ventricular site, however, increased the yield of ventricular tachycardia induction by 24% in this patient population.

Relation of Arrhythmia Induction to Periinfarction Arrhythmias

Patients 4, 6, 13, 20 and 23 had ventricular tachycardia and fibrillation complicating the initial 24 hours of their myocardial infarctions. Patients 4, 6 and 23 had inducible ventricular tachycardia, whereas patients 13 and 20 did not. There was no significant difference in the incidence of inducible ventricular tachycardia in patients who had periinfarction

TABLE 1.—*Patient Characteristics in a Study of Patients With Myocardial Infarction (MI)*

Patient Number	Age, Sex	MI Site	Peak CK, IU	β-Blockers	Antiarrhyth Drugs	Long-Acting Nitrates	Calcium Antag	Wall Motion Abnorm	Ejection Fraction	F-U, Mo	VT Induced	Morphology	Induction Mode	Postevent: UA-MI	CABG	Sudden Death/VT	Survived	Nonsudden Death	Antiarrhyth Drugs
1	70 M	Nontransmural	700	No	Yes	Yes	Yes	Yes	0.41	1	Yes*	LBBB	TES	...	...	Yes	...	...	...
2	52 M	Anterior	4,000	No	No	No	No	Yes	0.25	19	Yes	Pleo	QES	UA	...	Yes	Yes	...	Yes
3	60 M	Nontransmural	1,980	Yes	No	No	No	Yes	0.65	22	No	...	...	...	...	...	...	...	...
4	60 M	Inferopost	5,040	No	No	Yes	No	Yes	0.42	21	Yes	RBBB	TES	UA	Yes	...	...	...	...
5	65 M	Inferior	726	Yes	No	Yes	No	Yes	0.50	20	Yes	Pleo	QES	...	...	...	...	...	...
6	52 M	Inferior	750	No	No	Yes	No	Yes	0.50	21	Yes	Pleo	TES	...	...	...	...	...	...
7	57 M	Nontransmural	618	Yes	No	Yes	No	Yes	0.59	20	Yes*	Pleo	TES	...	...	...	...	...	...
8	60 F	Nontransmural	1,422	No	No	Yes	No	Yes	0.27	2	Yes	RBBB	QES	UA	Yes	...	...	Noncardiac	...
9	55 M	Nontransmural	496	Yes	No	Yes	Yes	Yes	0.33	19	Yes	Pleo	TES	...	...	...	...	...	...
10	55 M	Inferior	826	Yes	No	Yes	No	Yes	0.47	20	Yes*	Pleo	TES	UA	...	...	...	...	...
11	39 F	Anterior	2,800	Yes	No	No	No	Yes	0.51	12	No	...	...	UA	...	...	...	...	...
12	65 M	Anterior	670	No	No	No	No	Yes	0.48	23	Yes*	RBBB	QES	MI	...	...	...	...	Yes
13	37 M	Inferior	936	Yes	No	No	No	Yes	0.37	Lost	No	...	...	...	...	...	...	...	...
14	51 M	Anterior	...	Yes	No	Yes	No	Yes	0.34	21	Yes	Pleo	TES	...	Yes	...	...	...	...
15	56 M	Lateral	304	Yes	No	Yes	No	No	0.68	3	Yes*	RBBB	DES	...	Yes	...	...	Cardiac	...
16	34 M	Anterior	1,001	Yes	No	Yes	Yes	Yes	0.51	19	Yes	Pleo	QES	...	...	...	...	...	...
17	64 M	Anterior	1,156	Yes	No	No	No	Yes	0.34	18	Yes	LBBB	QES	...	...	...	...	...	...
18	61 M	Anterior	1,026	Yes	No	No	No	Yes	0.31	16	Yes	Pleo	QES	...	...	...	...	...	...
19	58 M	Nontransmural	...	Yes	No	Yes	No	No	0.66	26	Yes*	Pleo	QES	...	...	...	...	Noncardiac	...
20	55 M	Nontransmural	468	Yes	No	No	No	Yes	0.42	25	No	...	...	...	...	...	...	...	...
21	37 M	Nontransmural	293	Yes	No	Yes	No	Unknown	0.62	19	Yes	Pleo	QES	...	...	...	...	...	...
22	60 M	Inferolat	878	Yes	No	Yes	No	Yes	0.37	22	Yes	Pleo	QES	...	...	...	...	...	...
23	74 M	Anterior	1,125	Yes	No	No	No	Yes	0.32	22	Yes*	RBBB	TES	...	...	...	...	...	...
24	69 M	Nontransmural	248	No	Yes	Yes	No	No	...	5	Yes	Pleo	TES	...	...	Yes	...	...	...
25	57 M	Inferior	1,145	Yes	No	Yes	No	Yes	0.45	17	Yes*	VF	QES	UA	Yes	...	...	...	...
26	58 M	Inferior	2,550	Yes	No	Yes	No	Yes	0.60	21	Yes*	Pleo	TES	...	...	...	...	...	...
27	45 M	Inferior	1,017	Yes	No	Yes	No	Yes	0.62	19	Yes	Pleo	QES	MI	Yes	...	...	...	...
28	65 M	Unknown	2,205	No	No	Yes	No	Yes	0.24	3	Yes*	RBBB	TES	...	Yes	...	...	Noncardiac	...
29	72 M	Nontransmural	2,350	Yes	No	No	No	Yes	0.49	13	Yes	Pleo	QES	...	...	Yes	...	...	...
30	68 M	Nontransmural	700	Yes	No	Yes	Yes	Yes	0.41	13	Yes	Pleo	QES	...	...	...	...	...	...
31	64 M	Anterior	1,294	Yes	No	Yes	No	Yes	0.41	19	Yes*	Pleo	TES	...	...	...	...	Cardiac	...
32	67 M	Nontransmural	1,300	No	No	No	No	Yes	0.51	13	No	...	...	...	...	...	...	...	...
33	57 M	Anterior	335	Yes	Yes	Yes	No	Yes	0.71	24	No	...	...	...	...	...	...	...	Yes
34	70 F	Nontransmural	350	Yes	No	No	No	Unknown	...	21	Yes	Pleo	DES	...	...	...	...	...	...
35	61 M	Anterior	2,450	Yes	No	Yes	No	Yes	0.35	16	Yes	Pleo	QES	...	...	...	...	...	...
36	58 M	Inferolat	1,100	Yes	No	Yes	Yes	Yes	0.47	13	Yes	Pleo	QES	...	...	...	...	...	...
37	69 M	Inferior	2,960	No	No	Yes	No	Yes	0.42	13	Yes	Mono	QES	UA	...	...	...	...	Yes
38	50 M	Inferior	1,504	Yes	No	No	No	Yes	0.53	16	Yes*	Mono	TES	...	...	...	...	...	...
Total																			
38	58 [±9.8]†	F=3 M=35	1,353 [±1,066]†	Yes=28 No=10	Yes=3 No=35	Yes=25 No=13	Yes=5 No=33	Yes=33 No=3	0.46 [±0.12]†	16.6 [±6.5]†				UA=7 MI=2	7	4	1	NC=3 C=2	4

Abnorm = abnormalities, Antag = antagonists, Antiarrhyth = antiarrhythmic, CABG = coronary artery bypass grafting, CK = creatine kinase, DES = double extrastimuli, F-U = follow-up, Inferolat = inferolateral, Inferopost = inferoposterior, LBBB = left bundle branch block, Mono = monomorphic rhythm, Pleo = pleomorphic rhythm, QES = quadruple extrastimuli, RBBB = right bundle branch block, TES = triple extrastimuli, UA = unstable angina, VF = ventricular fibrillation, VT = ventricular tachycardia

*Sustained ventricular tachycardia.
†Mean (± standard deviation).

ventricular arrhythmias compared with those who did not (P = not significant). None of these patients have subsequently had ventricular tachycardia or fibrillation; no follow-up data are available on patient 13, however.

Rhythm Morphology

In the 32 patients in whom ventricular tachycardia was induced, the mean cycle length was 213 ms (shortest R-R interval) with a range of 160 to 260 ms. The ventricular tachycardia had a right bundle branch block morphology in 6, left bundle branch block morphology in 2, was a nonlateralizing monomorphic rhythm in 2 and was polymorphic in 22 cases. Of 17 of the tachycardias induced by four extrastimuli, 14 (82%) were pleomorphic. The ventricular tachycardia required DC cardioversion in eight patients. The remainder were converted with burst ventricular pacing. The mean ejection fraction in patients with monomorphic sustained ventricular tachycardia was 42% versus 53% in patients with pleomorphic sustained rhythms (not significant).

Holter Monitor Data

Holter monitor data were obtained in 23 of 38 of the patients. Ventricular tachycardia was induced with electrophysiologic testing in 13 of the 15 patients with Lown class 1B or less ventricular ectopy[16] (87%) as compared with induction in 100% of the 8 with "frequent" or complex ventricular ectopy, Lown class 2 to 4A ($P > .05$). None of the patients had Lown 4B or 5 ventricular arrhythmias.

Effects of β-Blocking Agents, Antiarrhythmia Agents and Calcium Channel Blockers

Of the 38 patients, 28 were on β-blocker therapy. Ventricular tachycardia was induced in 24 (86%) as compared with induction in 9 of 10 (90%) patients who were not taking β-blockers (not significant).

As noted previously, three patients were receiving antiarrhythmic agents at the time of the studies. Patients 1 and 24 were taking quinidine and procainamide (respective serum concentrations of 3.8 and 1.0 mg per dl). Sustained monomorphic ventricular tachycardia was induced with three extrastimuli in the former and a ten-beat run of polymorphic nonsustained ventricular tachycardia was induced with three extrastimuli in the latter. Patient 33, who was not inducible, received phenytoin as therapy for a concomitant seizure disorder (serum concentration of 17 mg per dl). Calcium channel blockers were used in five patients, all of whom had inducible ventricular tachycardia.

Clinical Status After Discharge

Follow-up information is available on 37/38 patients (98%; Figure 2, Table 1) with the mean duration of follow-up being 16.6 months ± 6.5 (standard deviation; range 1 to 27 months). All surviving patients have been followed a minimum of 12 months.

There have been eight deaths, three of which were sudden. One additional patient (patient 2) survived an episode of sustained ventricular tachycardia ten months after his original electrophysiologic study. The sudden deaths occurred at 1, 5 and 13 months following their electrophysiologic studies. Of the five nonsudden deaths, two were cardiac (patients 15 and 31) and three noncardiac (patients 8, 19 and 28) in origin. Patient 15 died during a coronary bypass surgical procedure. Patient 31 died of complications of a recurrent myocardial infarction following a cerebrovascular accident.

As can be seen in Table 1, several patients have been admitted in the interim with recurrent unstable angina or myocardial infarction and seven of the patients have gone on to a coronary artery bypass operation. In three patients antiarrhythmic drug therapy has been instituted, in two because of supraventricular arrhythmias (patients 12 and 37) and in one because of ventricular tachycardia ten months after the study (patient 2).

Programmed electrical stimulation (Table 2) with a positive test defined as induction of ventricular tachycardia was overall a sensitive (100%) predictor of clinical sudden death or ventricular tachycardia. Specificity was only 15% and predictive accuracy was 24%.[17] With three or fewer extrastimuli, specificity improved but sensitivity fell. Induction of *sustained* ventricular tachycardia (Table 1) had only a 25% sensitivity for subsequent sudden death.

Life-table analysis showed that programmed ventricular stimulation, regardless of the number of extrastimuli used,

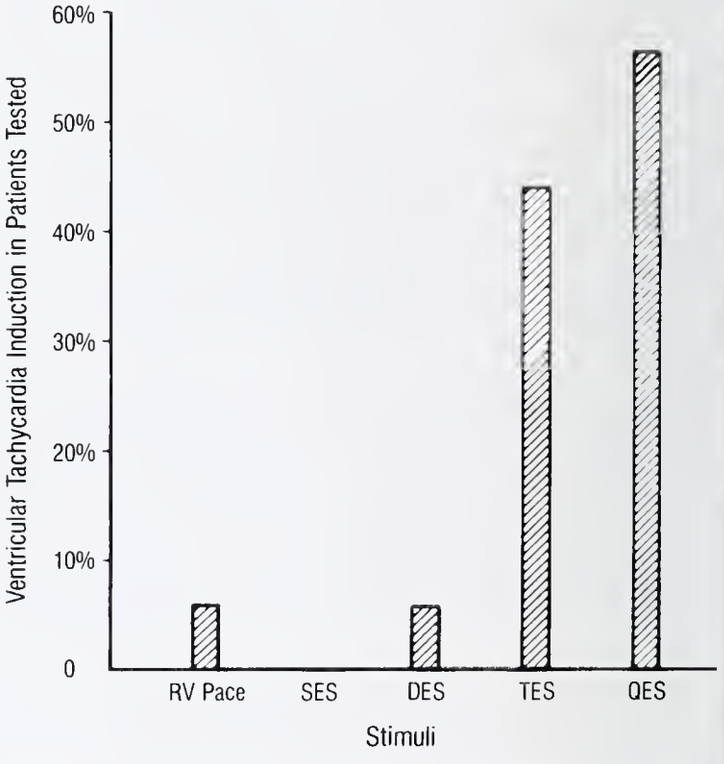

Figure 1.—Ventricular tachycardia induced according to number of stimuli used. RV = repetitive ventricular, SES = single extrastimulus, DES = double extrastimuli, TES = triple extrastimuli, QES = quadruple extrastimuli

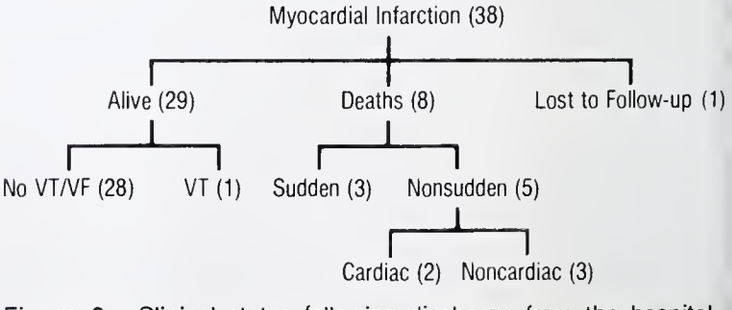

Figure 2.—Clinical status following discharge from the hospital. VT/VF = ventricular tachycardia or fibrillation.

did *not* discriminate those who died suddenly or nonsuddenly from those who did not (Figure 3). The ejection fraction was not a useful predictor of sudden or nonsudden death when analyzed independently or with other variables.

Relation of Sudden Death or Ventricular Tachycardia to Holter Monitor Data and Use of β-Blockers

All four patients who in follow-up either died suddenly (three) or were resuscitated from ventricular tachycardia (one) had inducible ventricular tachycardia. Holter monitoring had elicited frequent or complex ventricular premature beats in two; the other two were not monitored. One out of four were taking β-blockers at the time of their events. One had the use of β-blockers discontinued because of congestive heart failure or lung disease. Of these four patients, patient 24 was the only one receiving antiarrhythmia therapy (procainamide concentration <1 mg per dl), on which he had been placed for treatment of paroxysmal supraventricular tachycardia. Only 1 of 28 (4%) patients taking β-blockers subsequently died suddenly.

Complications

There were no significant complications associated with this protocol.

TABLE 2.—*Prediction of Sudden Death or Ventricular Tachycardia By Varying Number of Extrastimuli*

	Sensitivity, Percent	Specificity, Percent	False-Positive, Percent	False-Negative, Percent	Predictive Accuracy, Percent
SES	0	100	0	11	89
DES	0	94	100	11	84
TES	50	61	87	9	59
QES	100	15	88	0	24

SES = single extrastimulus, DES = double extrastimuli, TES = triple extrastimuli, QES = quadruple extrastimuli

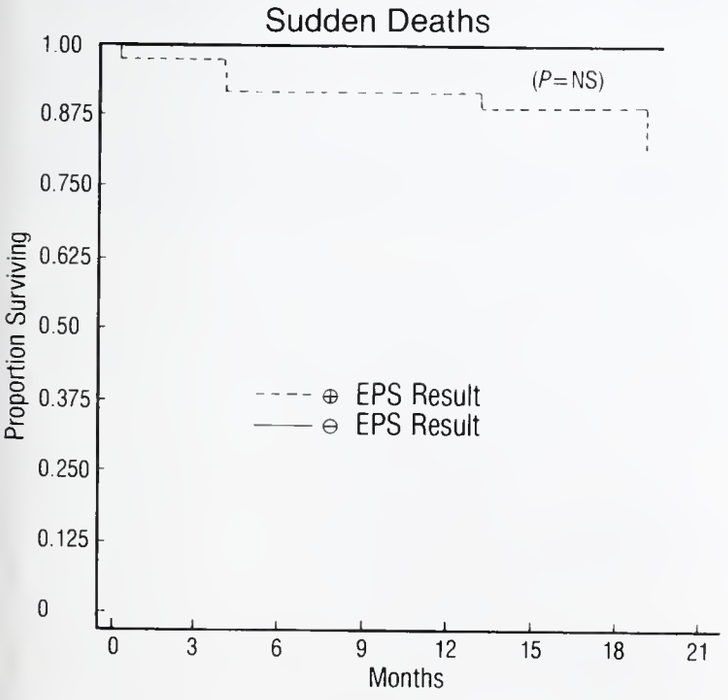

Figure 3.—Cumulative survival for sudden deaths for patients plotted until the number at risk in each group equals 10. EPS = electrophysiologic stimulation, NS = not significant

Discussion

In survivors of a recent myocardial infarction, ventricular tachycardia was induced in 84%. This was the case despite the exclusion of those who had clinical ventricular tachycardia following the infarction. The sensitivity of this protocol for predicting sudden death or ventricular tachycardia was 100% overall. The specificity, however, was poor (15%), with an 88% false-positive rate and 24% predictive accuracy. Using two or even three extrastimuli, as done in many laboratories, also resulted in an unacceptably poor sensitivity, although specificity was enhanced. β-Blocking therapy was instituted before the electrophysiologic study whenever possible (28 of 38 patients). This distinguishes the present study from others evaluating electrophysiologic testing. The decision to use these drugs was made because of the high likelihood that patients with myocardial infarction will be discharged on a regimen of these agents because of their efficacy in decreasing subsequent cardiac events following myocardial infarction.[18]

Other investigators have evaluated the prognostic value of programmed electrical stimulation following myocardial infarction, but the protocols have differed.[7-12,19] Some have concluded that the study lacks prognostic value,[10-12,19] whereas others are more optimistic about its use.[7-9,20] Of the latter, Richards and colleagues have studied the largest number of patients.[9] In their patients, the predictive accuracy of a negative study was 98%, thereby clearly identifying a low-risk group. The predictive accuracy of a positive test for defining subsequent sudden death was only 32%—a finding similar to that of the present study.

Using an aggressive stimulation protocol, ventricular tachycardia was induced in 84% of our patients. This protocol was very sensitive in identifying patients at risk for sudden death, but was unacceptably nonspecific in that many patients not at risk for sudden death would require therapy to protect those patients at greatest risk. If serial electrophysiologic testing were used to select the treatment regimen for the patients with inducible myocardial infarction in the present study, 32 patients would require serial drug testing to adequately protect the 4 patients who eventually died suddenly or in whom ventricular tachycardia developed. Even in the population studied by Richards and co-workers, 38 patients with inducible ventricular tachycardia would require therapy in an attempt to protect the 8 patients who eventually died suddenly.[9]

In the present study, all patients underwent one, two and then three extrastimuli before a fourth extrastimulus was used. Two extrastimuli identified none of the patients at risk, and even a third extrastimulus would have missed half of the patients who died suddenly or in whom ventricular tachycardia developed. We therefore conclude that programmed electrical stimulation is not a useful test for identifying patients at risk for sudden death or ventricular tachycardia in this population.

Limitations of the Present Study

Only 35% of patients eligible for the study at this hospital agreed to this invasive research protocol, and it is possible that the findings do not reflect those who would be found in myocardial infarction survivors in general. The incidence,

however, of sudden death and ventricular tachycardia in follow-up is similar to comparable patient populations[1] and suggests that the findings are valid.

Some of the studies were done with the patients off their β-blocker therapy (ten patients). It is of interest that three of the four patients who had sudden death or ventricular tachycardia in follow-up were unable to take β-blockers for clinical reasons. It is possible that there would have been a higher incidence of sudden death if no patients were receiving β-blockers. For ethical reasons, however, this was not incorporated in the protocol. Additionally, three patients were taking standard antiarrhythmic drugs for reasons other than ventricular tachycardia at the time of the protocol. Interestingly, neither seemed to affect the inducibility of the arrythmias but perhaps could have exacerbated or suppressed arrhythmia induction.

A stimulation current of 5 mA was used, which could increase ventricular tachycardia induction. Although this is higher than that used in some centers, it is not out of line with the protocols of other laboratories.[21,22] Three and four extrastimuli were used in the present protocol, which have been reported to produce nonclinical arrhythmias in some studies[19] but have been clinically useful in other series.[23] In a recently published study of patients with sustained ventricular tachycardia or fibrillation,[24] the use of a fourth extrastimulus increased the induction of sustained ventricular tachyarrhythmias from 48% to 64%. In this study in which all patients underwent two baseline induction studies, nonreproducibility with three or four extrastimuli was not significantly greater than when only two extrastimuli were used. Again, if only two extrastimuli were used in the present study, none of the patients who subsequently died suddenly would have been identified.

The number of patients studied in the present protocol was relatively low, rendering the conclusions subject to a type II statistical error. This might be minimized by a large cooperative study using a uniform stimulation and treatment protocol. Nevertheless, the 84% rate of ventricular tachycardia induction seen in the present study strongly suggests that ventricular tachycardia induction soon after a myocardial infarction is a relatively nonspecific finding.

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The Syndrome of Paroxysmal Positional Vertigo

A Review

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Paroxysmal positional vertigo is one of the most common types of vertigo. When there are no other neurologic abnormalities and the vertigo occurs only with changes in head position and is associated with a direction-fixed fatiguing nystagmus that has a latency of onset and a brief duration, the term "syndrome of paroxysmal positional vertigo" applies. This syndrome is usually idiopathic and is rarely seen in association with central nervous system disease. The diagnosis usually can be made on the basis of a careful history and physical examination without costly laboratory procedures. Habituation training may be therapeutic.

(Mohr D: The syndrome of paroxysmal positional vertigo—A review. West J Med 1986 Nov; 145:645-650)

A common clinical challenge in the practice of medicine is the evaluation of vertigo (the illusion of self- or environmental movement). Often this vertigo is described as occurring only with head movement or position changes. When an examination of a patient in various head-hanging positions[1-3] elicits the symptom of vertigo associated with the finding of nystagmus,[4] consideration must be given to a diagnosis of the syndrome first described by Bárány[5] and variously termed "positional nystagmus of the benign paroxysmal type,"[2] "paroxysmal positional nystagmus,"[3] "benign paroxysmal positional nystagmus,"[6] "paroxysmal positional vertigo,"[7] "benign paroxysmal positional vertigo"[8] and "cupulolithiasis."[9]

Paroxysmal positional vertigo makes up about 25% of cases of vertigo[10] and constitutes the largest subset of cases of positional vertigo.[4,11] The term is often loosely applied to various symptoms; as described by Dix and Hallpike, however, the syndrome includes the following criteria[2]: (1) a clinical history of episodes of vertigo occurring only with changes in head position; (2) nystagmus that is elicited in a head-hanging position and is usually direction-fixed and rotatory with a horizontal and vertical component; (3) a latent period of 5 to 15 seconds before the nystagmus occurs; (4) a decrease in intensity of the nystagmus after 2 to 30 seconds[2,3] (the descriptive label "paroxysmal" is derived from items 3 and 4)[4]; (5) frequent reversing of the direction of nystagmus with assumption of the sitting position, and (6) fatigability of the nystagmus and vertigo when the subject is repeatedly returned to the provocative head-hanging position.

In this review, the term "syndrome of paroxysmal positional vertigo" will be used to describe the syndrome in which these criteria apply. Many reports that include patients with directions of nystagmus other than as described in item 2 consider these cases separately.[3,12-14] Unfortunately, all six of these criteria are rarely specified as necessary for inclusion of a case for analysis in reports of patients with this syndrome.[2-4,6-8,12,14] In one report, the clinical history was used as its basis[7]; others reviewed only cases with the characteristic paroxysmal positional nystagmus.[3,4,12,14]

Patients who have the syndrome of paroxysmal positional vertigo experience episodes of vertigo of short duration when they turn from side to side in bed, get out of bed, bend their head back (such as to shave) or move their head rapidly horizontally or vertically.[2,8] The vertigo may be accompanied by nausea, and, during periods of frequent episodes, patients may complain of unsteadiness or nausea between episodes.[7,8] Intervals between episodes may range from hours to years. Although the syndrome may be found in association with other otologic or central nervous system diseases or trauma, it usually occurs as a benign disorder in persons who are between the ages of 40 and 70 years.[7,15] Verifying the presence of all the criteria when this diagnosis is suspected is often difficult because the attacks may have subsided by the time of the initial examination. In most of these patients, an attack can be elicited by positional maneuvers if the patient is reexamined at a later date during a recurrence of symptoms.[7]

Clinical Evaluation and Diagnosis

Positional Maneuvers

Various positional maneuvers can be used clinically to elicit the nystagmus and vertigo. Nylén described a head-hanging maneuver in the sagittal plane and a maneuver in the

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frontal plane in which the examiner starts the patient from a supine position and sequentially turns the patient's head to the right and then to the left lateral position.[1] Dix and Hallpike used a maneuver that starts with the patient in a sitting position with the head turned to one side and the gaze fixed on the examiner's forehead.[2] The examiner then grasps the patient's head firmly and briskly lays the patient supine with the head lowered 30 degrees below the level of the couch and turned 30 degrees to one side (Figure 1, left). The patient is then allowed to sit up, and the maneuver is repeated with the head turned to the other side.

The peak velocity of the slow component of the nystagmus is positively correlated with the speed of the positioning maneuver, and the latency is inversely correlated. If positioning is done too slowly, the nystagmus is not induced.[15] The position change should be accomplished in about 2 seconds.

Direction of Associated Nystagmus

The nystagmus seen in this syndrome is rotatory with a vertical component; both beat toward the undermost ear in the provocative head-hanging position (Figure 1, right). A horizontal component that is dissociated with the ipsilateral eye beating away from the down ear and the contralateral eye beating toward the down ear also has been noted.[15] Defining the vertical component by electronystagmography has been suggested as being helpful in differentiating central nervous system causes that beat downward from benign causes of paroxysmal positional nystagmus.[15]

Determining the direction of nystagmus in different head-hanging positions may be important. When the direction of paroxysmal positional nystagmus changes in different head-hanging positions, central lesions may more likely be present than when it is direction-fixed.[3] In one report, direction-fixed cases were evaluated separately and 3.6% were found with central lesions compared with 30% in a non-direction-fixed group with paroxysmal positional nystagmus.[12] In the vast majority of reported cases with the syndrome of paroxysmal positional vertigo, the nystagmus is direction-fixed as required to fulfill the original definition.[2,4]

Use of Electronystagmography With Caloric Testing in Diagnosing Benign Paroxysmal Positional Vertigo

Caloric findings are of limited value in the clinical assessment of patients with suspected benign paroxysmal positional vertigo. Test results are usually normal[2] but may be abnormal.[3,7]

Associated Disorders

Once the clinical criteria for defining the syndrome of paroxysmal positional vertigo have been met, it is important to consider whether the syndrome is idiopathic or occurring in association with a central nervous system or peripheral disorder. It is most often idiopathic (Table 1) and the decision to evaluate the patient further should be based on the frequency of associated diseases, the nature of the associated diseases and the extent to which a history or physical examination can exclude their presence reliably without further costly laboratory procedures.

Associated Central Disorders

When all of the criteria for the syndrome are included, none of the 100 patients described by Dix and Hallpike and

TABLE 1.—*Disorders Associated With Paroxysmal Positional Vertigo*

	Katsarkas and Kirkham[7]		*Harrison and Ozsahinoglu*[12]	
Disorder	*Number*	*(Percent)*	*Number*	*(Percent)*
Idiopathic	169	(66)	220	(60)
Head injury	43	(17)	85	(23)
Ear diseases†	29	(11)	13	(4)
Sinus infection	0	...	9	(2)
Cervical spondylosis	0	...	5	(1)
Central nervous system	6	(2)	13	(4)
Other	8*	(3)	20	(5)
Total	255		365	

*Eight cases of non-direction-fixed nystagmus.
†Vestibular neuronitis, otosclerosis, poststapedectomy, chronic serous otitis media, sudden hearing loss, Meniere's disease, sudden change in ear pressure, "allergy."

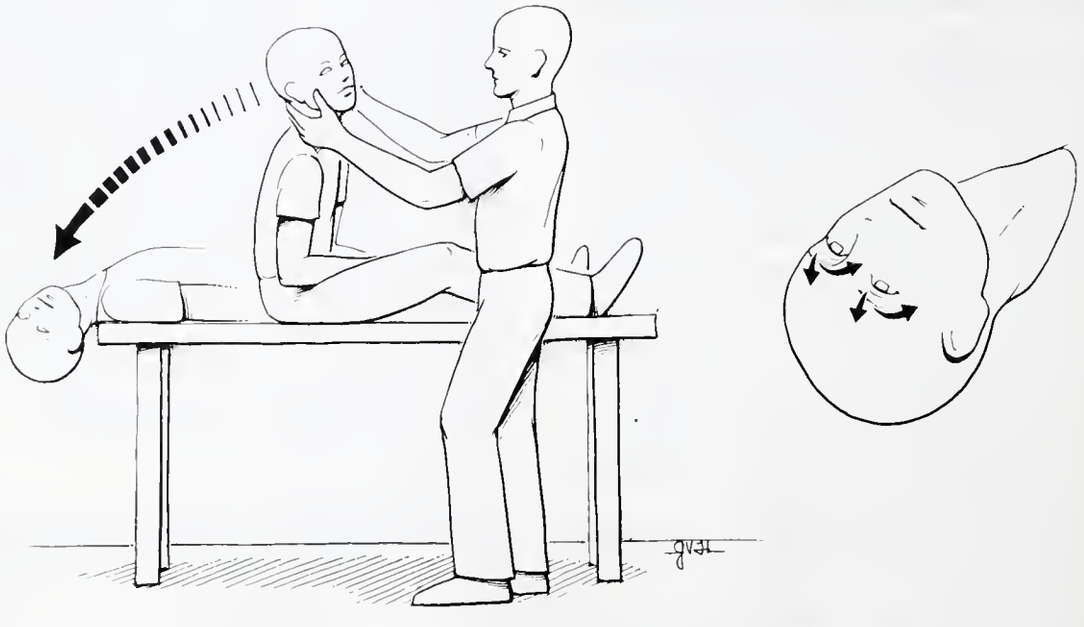

Figure 1.—Left, Right head-hanging maneuver as described by Dix and Hallpike.[2] **Right,** Direction of rotatory nystagmus in right head-hanging position.

none of the 114 described by Cawthorne had central pathologic lesions.[2,4]

In some reports, however, central pathologic lesions have been present in patients with all of the criteria; thus, the term "benign" may be a misnomer. In 255 patients reviewed with this syndrome, a meningioma in the right cerebellar hemisphere may have caused the disorder in 1 patient.[7] In another review of 365 patients, 2.2% had a diagnosis of arteriosclerosis of the brain stem, and 1.4% were said to have other central lesions.[12] Details of the diagnostic evaluation to confirm the central pathologic lesion and its relationship to paroxysmal positional vertigo were included in only one of the cases, however. Similarly, only 1 of 40 of the direction-fixed cases reported by Stahle and Terins had a central pathologic lesion.[3] Watson and co-workers reported four cases in which patients with brain tumors presented with symptoms suggesting a diagnosis of benign paroxysmal positional vertigo.[16] Three of the patients did not have associated neurologic symptoms and two had a latency of onset of the positional nystagmus and fit the diagnostic criteria. One other case has been reported in which a cerebellar tumor was found to be the cause of the syndrome.[17]

In contrast to the negligible incidence of central lesions in most reports of "benign" paroxysmal positional vertigo is one series in which 11 of 43 patients had a central cause for a direction-fixed paroxysmal positional vertigo that included both latency of onset and fatigability of the nystagmus.[14] This high percentage possibly resulted from the selective exclusion of "idiopathic" cases and inclusion only of cases with "an established clinical diagnosis" and possibly associated neurologic signs and symptoms.

Other cases mentioned in the literature as being associated with a central or toxic cause do not fulfill the detailed criteria for the syndrome.[13,18-22] For example, one reported case of transient positional nystagmus after cerebellar infarction was also associated with spontaneous nystagmus[20] and thus does not fit the complete definition. Dayal and associates noted paroxysmal positional nystagmus in patients with barbiturate overdosage.[13] Because the symptoms obviously were drug related, however, this is not a situation in which a physician must decide on the use of further laboratory tests to exclude an associated central lesion. Thus, although a rapidly occurring, persistent, direction-changing, nonfatiguing, positional vertigo is common with central lesions,[3,7,12] the paroxysmal positional vertigo that fits the initially listed criteria is usually not of central nervous system origin, except in a case of obvious drug overdosage or perhaps in the presence of associated neurologic signs and symptoms.

Associated Peripheral (Non-Central Nervous System) Disorders and Head Injury

Benign paroxysmal positional vertigo can also occur in association with peripheral disorders and head injury. About 30% to 50% of patients with the syndrome have head trauma or ear and vestibular disease.[2-4,7,12] Causes found in two large series of cases included head injury, ear diseases, systemic degenerative disease, sinus infection, dental disease and cervical spondylitis (Table 1).[7,12] In rare cases, acoustic neuromas have been reported to produce the syndrome.[14,21] Although no information is available to evaluate what tests are necessary to diagnose these associated disorders, it is evident from Table 1 that careful history taking and otologic and audiologic evaluations usually should establish the presence of an associated peripheral disorder or head injury.

Pathophysiology

Establishing a unifying pathophysiologic mechanism for the syndrome of paroxysmal positional vertigo may not be

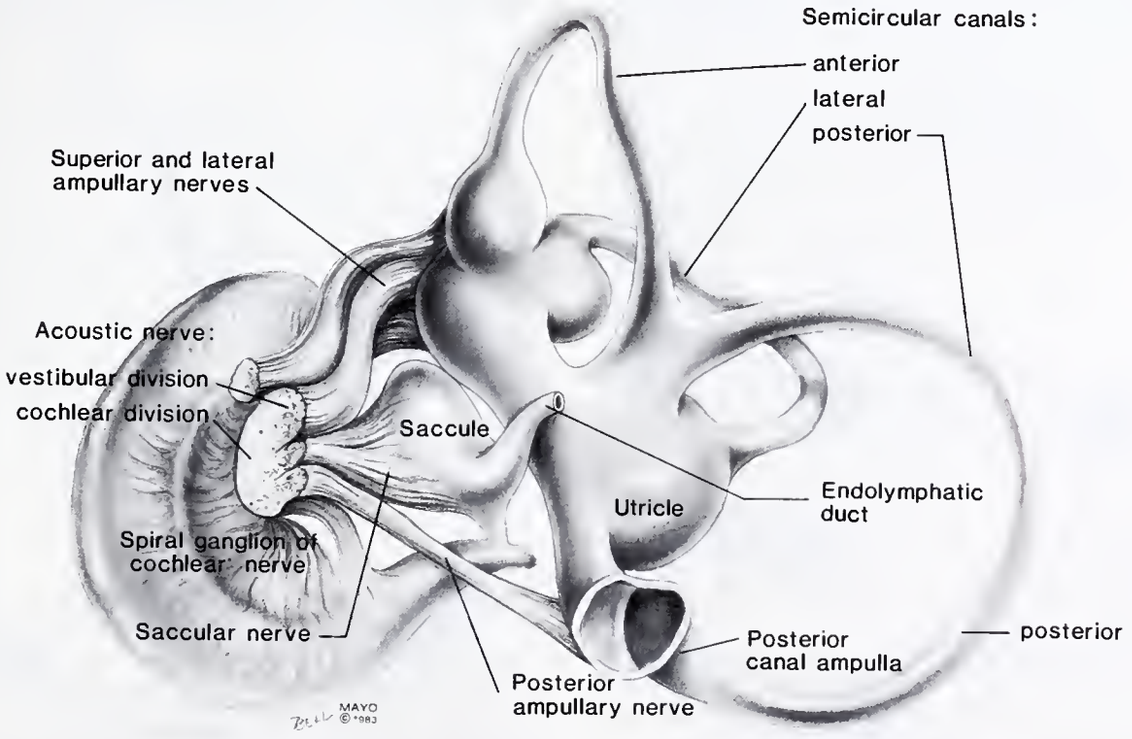

Figure 2.—Right inner ear, medial view, showing relationship of posterior canal and ampulla to labyrinth. Reproduced by permission of the Mayo Foundation.

possible. In regard to the very few cases associated with central pathologic conditions, it is known that lesions of the nodulus of cats can produce a positional nystagmus that decays in the provocative position.[23] The nystagmus, however, becomes compensated for by ten days in most animals and does not recur. Also, although the nystagmus may fit the definition of the syndrome, Baloh and colleagues have noted differences in electronystagmographic recordings between cases with cerebellar lesions and their usual cases with the syndrome.[15]

Because the progression, over time, from positional nystagmus to paroxysmal positional nystagmus has been shown in association with some cases of central and peripheral lesions,[13,14] some investigators have postulated that this spectrum of nystagmus—from spontaneous to positional to paroxysmal positional—represents a continuum of compensation by the vestibular system to an injury.[14]

A likely mechanism for many of the idiopathic cases of this syndrome in which no otologic disease is evident by conventional examination is cupulolithiasis. One theory is that sediment or statoconia (otoconia) come to lie in the posterior semicircular canal. This may happen as a spontaneous degenerative change in the labyrinth as a consequence of trauma or due to otitis media, a surgical procedure or occlusion of the anterior vestibular artery.[24,25] This sediment then comes into anatomic relationship with the cupula of the canal (Figures 2 and 3).[9] The hypothesis that the otoliths play a role is supported by the finding of unilateral degeneration of the utricular macule at autopsy in typical cases.[2,25] Basophilic deposits on the cupula of the posterior semicircular canal[9,24] and displaced statoconia[26] have been detected at autopsy in patients who had had symptoms of benign paroxysmal vertigo. Such findings have not been substantial in degree or number in control subjects. Because the posterior canal is in the most dependent position of the vestibular organ, displaced statoconia or debris is thought to collect in it or on the cupula (Figure 3). The normal density of the cupula is equal to that of the endolymph; thus, it is usually insensitive to gravity. With attached debris or with endolymph currents caused by loose statoconia, however, the posterior canal may be stimulated by a change in the head position (Figure 4), and nystagmus and vertigo could ensue.

Experimental studies have shown that nystagmus occurs in the plane of the semicircular canal that is stimulated. For example, ampulofugal endolymphatic flow in the left posterior semicircular canal produces contraction of the ipsilateral superior oblique muscle and the contralateral inferior rectus muscle.[6] With gaze directed forward, this produces an oblique nystagmus with the fast component cephalad and a rotatory nystagmus with the fast component to the left. In the left head-hanging position, the posterior semicircular canal of the underlying ear assumes a superior relationship to the remainder of the vestibular labyrinth. It has been postulated that attached debris or endolymph currents in the posterior semicircular canal (Figure 4) can cause ampulofugal flow and a resultant characteristic rotatory nystagmus with the fast component toward the underlying ear.[6] The latency of the paroxysmal positional nystagmus and vertigo may be explained by the few seconds that must elapse for the mechanical changes of the cupula to occur. Intermittency may occur because occasionally the deposits may not be in a position to cause stimulation.[27] Transience or fatigability may eventuate because, even with continued cupular displacement, adaption may cause the nystagmus to subside gradually.[27] Similarly, if loose statoconia are the cause of cupular displacement, they may pass and allow the cupula to return to a neutral position; hence, the nystagmus would fatigue.

Regardless of whether or not the cupulolithiasis theory is correct, the posterior semicircular canal is implicated in the pathophysiology of most cases of benign paroxysmal positional vertigo because stimulation of the posterior ampullary nerve duplicates the nystagmus seen in the syndrome as de-

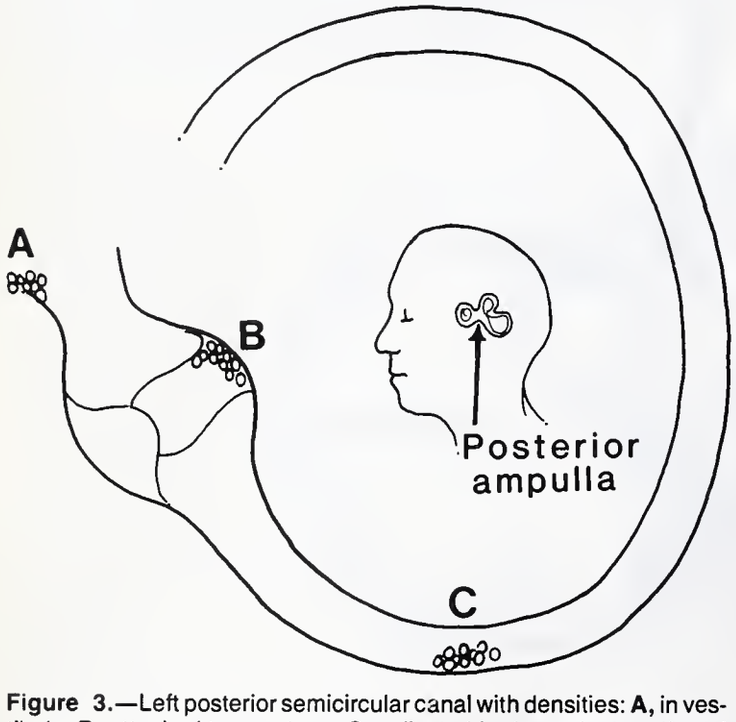

Figure 3.—Left posterior semicircular canal with densities: **A,** in vestibule; **B**, attached to cupula, or **C**, collected in dependent portion of canal (modified from Epley[8]).

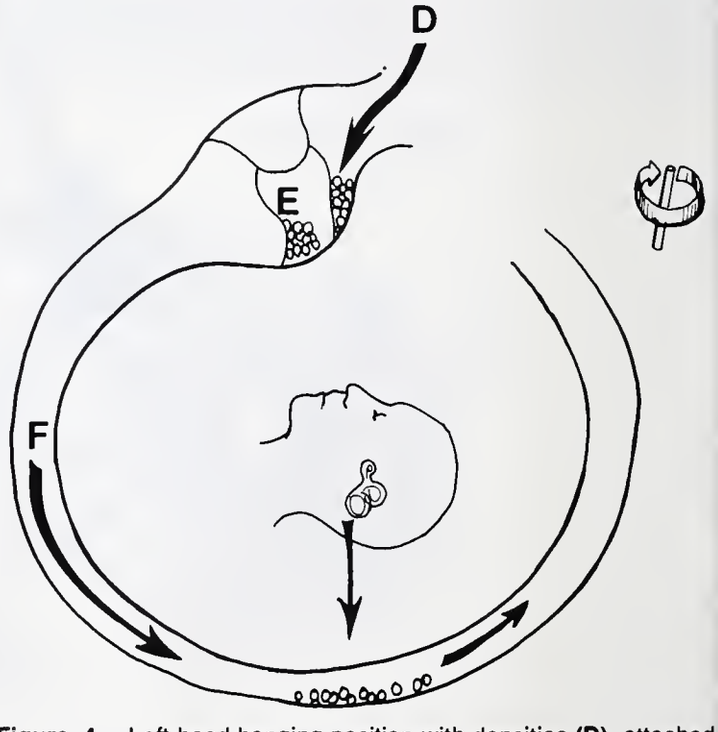

Figure 4.—Left head-hanging position with densities **(D)**, attached debris **(E)** or endolymph current **(F)** causing displacement of cupula (modified from Epley[8]).

scribed above, and ablation of this nerve relieves the symptoms and findings[28] as described below.

Therapy

Specific recommendations regarding therapy for benign paroxysmal positional vertigo are limited by a lack of pertinent controlled studies. Because studies in animals done with recordings from the vestibular nuclei have shown that certain drugs decrease the basal firing rate of these nuclei, there appears to be a rationale for the use of suppressant medications. Reviews of the use of antihistaminic, sympathomimetic and parasympatholytic agents in the management of vestibular vertigo, however, fail to define their clinical usefulness in this disorder.[29,30] Similarly, despite comparable effects on vestibular responses in the static state, benzodiazepines show no benefit over placebo when used in patients with paroxysmal positional vertigo.[31] Ototoxic agents are not used in cases of this relatively benign syndrome because of their bilateral and permanent effect on vestibular function.

Exercises involving a series of positional movements to improve the functional status in patients with positional vertigo have been described. After the head-hanging position that elicits symptoms of vertigo is identified, the patients repeat the provoeative maneuver five times in two to five sessions a day. In two series, more than 90% of patients had a decrease in symptoms or were symptom-free after a few days to a few months.[32,33] Although no control group was ineluded in either trial, the duration of symptoms was much shorter than that for placebo groups reviewed during drug trials[31] or for untreated patients.[32]

On rare occasions, symptoms have been thought to bc severe enough to warrant offering surgical labyrinthectomy or division of the vestibular portion of cranial nerve VIII.[11] The suecess of this approach to therapy has been used as evidence to support the labyrinthine origin of benign paroxysmal positional vertigo[8]—specifically, the posterior semicircular canal.[34] Transection of the nerve to the posterior ampulla (singular neurectomy) has been described as a means to relieve symptoms.[28,35] Although usually effective, the operation may be complicated by hearing loss.[8] A surgical therapeutic approach requires knowing which ear is involved.[36] Most investigators have found that, when other evidence of unilateral ear disease exists, the direction of nystagmus is toward the diseased ear when it is undermost.[2-4,9,35] If no otologic abnormality except vertigo is present, the side that is diseased must be inferred. A recent study, however, found that 44% of patients having a reduced vestibular response (suggesting a pathologic disorder in that ear) had nystagmus when that ear was up.[36]

Conclusions

The relatively common occurrence of symptoms suggesting the syndrome of paroxysmal positional vertigo requires that physicians be aware of its diagnostic features and understand when laboratory tests are required to exclude other diagnoses. Use of the terms "generally" and "frequently" by early authors to describe some of the features of this syndrome has led to some variation in cases and to differences in the frequency of serious associated diseases reported in the literature. It is generally accepted that the following criteria are required:

- A clinieal history of vertigo occurring only with changes in head position; and
- Nystagmus that is elicited in a head-hanging position, has a latency of onset and is 2 to 30 seconds in duration.

The following other criteria are variably required in cases reported in the literature, and their presence or absence may define subgroups of the syndrome.

- The direction of the nystagmus should be rotatory (upper pole of the eye beats toward the undermost ear) with an upbeating vertical component. Not enough data are available to determine if electronystagmographic documentation of this direction will be of benefit in distinguishing serious from benign causes of the syndrome. This direction is consistent with a pathologic condition in the posterior semicircular canal.
- The nystagmus should be direction-fixed. Cases in which the nystagmus changes direction in different head-hanging positions have a higher frequency of associated central neurologic lesions.
- The nystagmus should fatigue with repeated testing. This criterion has been postulated to distinguish fixed cupular lesions from loose otoconia,[27] but no systematic study has been done to determine whether it is required in the definition. Therefore, its presence should be noted but not required for diagnosing the syndrome.
- The nystagmus should change direction with resumption of the sitting position. Again, this criterion has not been uniformly used in the literature and should be noted but not required for diagnosis.
- Although not mentioned in the original definition, abnormal neurologic symptoms and signs should be absent. This would help to exclude cases of drug overdose or the rare case of a central neurologie disorder.

The syndrome is usually isolated or "idiopathic" but may be associated with peripheral otologic disorders or trauma and, rarely, may be associated with central neurologic disease. These central disorders cause the syndrome infrequently enough that a careful history and physical examination and consideration of possible associated otologic disorders are all that are required for diagnosis of the syndrome. Patients with the syndrome should be followed closely for the development of new signs or symptoms.

Although pharmaeologie and surgical therapy have been used to treat the syndrome in specific situations, a benign course warrants reassurance and a conservative approach. Habituation to the symptoms may occur more quickly with maneuvers designed to precipitate the symptoms on a daily basis.

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Smoking Habits Among Multiphasic Examinees, 1979 to 1984

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In tabulating the smoking habits of 95,744 residents of the San Francisco Bay Area, as reported between July 1979 and June 1984 at multiphasic health checkups, the prevalence of current smoking was found to be higher in men than in women aged 30 years and above, but in those younger than 30 the reverse was true. In every age group, compared with male smokers, female smokers tended to smoke fewer cigarettes per day, to inhale less and to smoke cigarettes with lower tar and nicotine yield. Blacks showed the highest percentage of smokers, whites were second highest and Asians were lowest, with Asian women being substantially lower than other race-sex groups. On average, white smokers smoked more cigarettes per day and inhaled more than did black smokers, but whites were more apt to smoke low-yield cigarettes. Compared with a 1964 to 1968 study in the same setting, there has been a decrease in the prevalence of cigarette smokers but, among smokers, a higher proportion in 1979 to 1984 smoked at least 20 cigarettes per day. During the 1979 to 1984 period, there were small downward trends in the prevalence of cigarette smoking in men and white women and in the prevalence of heavy smoking among male smokers, but there was no apparent increase in the use of lower-yield cigarettes by smokers. Although this study group contained relatively fewer smokers, most of the age, sex and racial differences and long-term trends parallel what has been observed nationally.

(Friedman GD, Sidney S, Polen MR: Smoking habits among multiphasic examinees, 1979 to 1984. West J Med 1986 Nov; 145:651-656)

Since July 1979, we have been conducting a prospective cohort study to determine the health effects of smoking low-yield cigarettes. Persons enter the study when they complete a detailed questionnaire about their smoking habits. This questionnaire is self-administered on a voluntary basis during multiphasic health checkups. Because the study group is large and heterogeneous with respect to ethnicity and socioeconomic status, we tabulated its responses regarding smoking habits as an indication of recent trends in smoking practices among blacks and whites in the San Francisco Bay Area.

Methods

An automated multiphasic health checkup (MHC) has been offered since 1964 to about 25,000 persons per year at each of two medical centers of the Kaiser Permanente Medical Care Program, one in Oakland and one in San Francisco.[1] The characteristics and correlates of the smoking habits among the program's subscribers who undergo these examinations have been studied extensively.[2-7] In general, the subscribers of this health maintenance organization come from almost all walks of life. Those who take these MHCs are also heterogeneous but, like others who desire health examinations, they tend to be better educated and more health-conscious.[2,8,9]

Starting in July 1979, examinees were asked to complete a supplementary questionnaire that explored their smoking habits in detail (shown, in part, in Figure 1). The tar yield was obtained from 1978 Federal Trade Commission estimates for each brand and type of cigarette.[10] Altogether 95,744 or 86.2% of the 111,104 examinees during the July 1979 to June 1984 study period completed this questionnaire. In mid-1980 the MHC was discontinued at the San Francisco facility. Findings regarding smoking habits refer to the entire study population, except that examination of time trends within the

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five-year period was restricted to subjects examined in Oakland. When subjects had more than one MHC, only the first was included in this analysis. All age adjustments were made with the direct method, with the age distribution of the entire study population used as the standard. Because the number of persons aged 80 years and over was small, they were excluded from the age-adjusted rates.

Results

Overall Smoking Habits

Among the men, the prevalence of current cigarette smoking rose from 19.8% in the 15- to 19-year age group to a peak of 32.0% in the 30- to 39-year-olds and a similar prevalence of 31.8% in the 40- to 49-year-olds (Table 1). Then there was a subsequent decrease with age to the low of only

If you have **never** used any tobacco product (cigarettes, cigars, tobacco pipe, chewing tobacco, snuff), check box below and then skip to questions 41-52.

1 ☐ Never used any tobacco product

If you have **ever** used any tobacco product (cigarettes, cigars, tobacco pipe, chewing tobacco, snuff), answer questions below, **then** answer questions 41-52.

1. **Have you ever smoked cigarettes regularly for at least one year?** (Here "regularly" means at least 5 cigarettes per week, almost every week)

1 ☐ Yes If Yes, answer questions 2-19 below.
2 ☐ No If No, skip to question 20.

3. **Do you still smoke cigarettes regularly?**

1 ☐ Yes
2 ☐ No, but I still smoke cigarettes occasionally
3 ☐ No, not at all

7. **How many cigarettes do you smoke per day, on the average? Or, if you have stopped smoking regularly, how many did you smoke, on the average, before you stopped?** (1 pack = 20 cigarettes) ___ ___ cigarettes per day

8. **What brand of cigarette do you usually smoke? Or, if you have stopped smoking, what brand did you smoke most recently?**_____

Are (were) these:
1 ☐ filtered
2 ☐ unfiltered

Are (were) these:
1 ☐ regular length (85mm)
2 ☐ king-size (100 mm)
3 ☐ long

Are (were) these:
1 ☐ mentholated
2 ☐ plain

14. **When you smoke, how often do you inhale the smoke? Or, if you have stopped smoking, how often did you inhale the smoke before you stopped?**

Check only one
1 ☐ All the time, each puff
2 ☐ Most of the time
3 ☐ Part of the time
4 ☐ Rarely
5 ☐ Never inhale

20. **Have you ever smoked cigars regularly for at least one year?** (Here "regularly" means at least two cigars per week, almost every week)

1 ☐ Yes If Yes, answer questions 21-30 below.
2 ☐ No If No, skip to question 31.

22. **Do you still smoke cigars regularly?**

1 ☐ Yes
2 ☐ No, but I still smoke cigars occasionally
3 ☐ No, not at all

31. **Have you ever smoked a tobacco pipe regularly for at least one year?** (Here "regularly" means at least two pipefuls of tobacco a week, almost every week)

1 ☐ Yes If Yes, answer questions 32-39 below.
2 ☐ No If No, skip to question 40.

33. **Do you still smoke a pipe regularly?**

1 ☐ Yes
2 ☐ No

Figure 1.—Depicted are items from the 1979 to 1984 tobacco questionnaire used for this study, selected and reproduced from a 52-item questionnaire used in an automated multiphasic health checkup.

8.5% among those aged 80 and over. Former smoking rose with age to a peak of 38.4% among 60- to 69-year-olds with a slight decline thereafter. The age trends for never smoked cigarettes and never smoked anything were similar to each other and were U-shaped, with the lowest prevalence in the 50- to 59-year group. Current cigar and pipe smoking were infrequent. The maximum age-specific prevalences were 3.5% for cigars among those aged 50 to 59 years and 3.8% for a pipe among those aged 60 to 69 years.

Among women, current cigarette smoking was also most prevalent in 30- to 39-year-old persons (30.0%), but all age groups from 15 through 49 years had about the same proportion of current smokers. This was followed by a pronounced decline with age to a low of 5.5% among those aged 80 and over. Cigarette smoking was more frequent in men than in women at all ages above 30 years but the opposite was true below age 30. As in the men, the age curve for former smoking was an inverted U shape with a maximum prevalence in the 60- to 69-year group. The prevalence of former smoking, however, was much higher in men than in women except below age 30, where men and women were quite similar. There was a considerably higher proportion of those who never smoked among the women at all ages above 30 years, the difference increasing with advancing age. In the 15- to 19-year age group, never having smoked was more common among men than women. Prevalences of cigar and pipe smoking among women are not shown in Table 1, as there were only 44 (0.1%) women who reported current cigar smoking and 21 (0.04%) who reported pipe smoking.

Racial Differences

Among both men and women, blacks showed the highest prevalence of current smoking (Table 2). The men of other and unknown race were second highest, whites third highest and Asians lowest with a prevalence of 61% of that of blacks. Among women, whites had the second highest prevalence and those of other and unknown race had the third highest. Asian women had a strikingly lower prevalence, only 30% of that of blacks. The within-race age patterns of current cigarette smoking were generally similar to those shown in Table 1 for all subjects combined. Deviations were found usually in groups where the numbers were small and the proportions therefore statistically unreliable.

More detailed breakdowns of smoking habits, to follow, were done only on all racial groups combined and on the two largest racial groups, blacks and whites.

Quantity Smoked

Overall the percentages of cigarette smokers who smoked at least 20 cigarettes per day (Table 3) peaked in the 50- to 59-year age group among the men and the 40- to 49-year age group among the women, with the 40- to 69-year groups all being close to peak, especially among the women. White cigarette smokers smoked considerably more cigarettes per day than blacks, on average, in every age group and among both sexes.

Inhaling

The questionnaire item on inhaling allowed respondents to choose among inhaling all the time, most of the time, part of the time, rarely or never (Table 4). The relative frequency of at least partially inhaling started at close to 100% in youth and gradually decreased with age. White men tended to exceed black men in reported inhaling only slightly in this tabulation. This racial difference, however, was more striking in a finer breakdown of inhalation categories in which 58.4% of all white men reported inhaling all of the time as compared with 45.3% of black men (age adjusted). Except for women in their 70s, the excess of inhaling in whites over blacks was somewhat greater in women than in men. Also, 52.1% of white women inhaled all the time as compared with 39.3% of black women (age adjusted).

Cigarette Yield

Based on the reported brand and type of cigarette usually smoked, smokers were classified as smoking cigarettes of

TABLE 1.—*Prevalence of Cigarette, Cigar and Pipe Smoking by Age and Sex in the Total 1979 to 1984 Study Population**

	Age, Years								
	15-19	20-29	30-39	40-49	50-59	60-69	70-79	80+	Total
Men									
Total number	1,076	8,047	11,694	7,576	6,713	4,963	1,587	223	41,879
Never smoked, %	75.4	59.1	42.8	35.2	31.2	33.2	39.9	48.9	42.3
Smokes cigarettes									
Never, %	75.8	60.0	45.4	38.8	36.2	39.2	47.4	55.2	45.7
Former, %	4.0	11.6	21.7	28.6	34.0	38.4	37.2	34.1	25.2
Current, %	19.8	27.7	32.0	31.8	28.7	21.1	14.0	8.5	28.2
Unknown, %	0.4	0.7	0.9	0.8	1.1	1.3	1.4	2.2	0.9
Currently cigar, %	0.1	0.7	1.4	2.3	3.5	3.2	3.1	0.0	2.0
Currently pipe, %	0.1	0.6	1.9	2.7	3.2	3.8	3.0	0.0	1.7
Women									
Total number	1,851	12,519	14,107	8,620	8,325	5,881	2,160	402	53,865
Never smoked, %	65.4	59.3	53.2	51.3	54.6	57.8	71.2	86.1	56.4
Smokes cigarettes									
Never, %	65.5	59.4	53.3	51.4	54.7	58.0	71.3	86.1	56.5
Former, %	4.8	10.6	16.2	18.5	18.5	20.4	16.4	8.2	15.6
Current, %	29.0	29.6	30.0	29.5	26.0	20.9	11.6	5.5	27.3
Unknown, %	0.7	0.4	0.5	0.6	0.8	0.7	0.7	0.2	0.6

*Cigarette, cigar and pipe smoking are tabulated independently without regard to one another.

either low yield (<15 mg tar), high yield (≥15 mg tar) or unknown yield, the last accounting for about 14% of smokers and varying little by sex and race (Table 5). Blacks were clearly less apt to smoke low-yield cigarettes than whites, and, except for blacks aged 15 to 19 years, men were less apt to smoke low-yield cigarettes than women. Except for some wide discrepancies in the few and therefore statistically unreliable 15 to 19 year-olds, there was little variation in preference for low-yield cigarettes by age.

Time Trends, 1979 to 1984

There were only small changes in the prevalence of cigarette smoking noted from year to year. Among white men the age-adjusted percentage of smokers was 26.5% in 1979 to 1980, 26.9% in 1980 to 1981, 25.6% in 1981 to 1982, 24.9% in 1982 to 1983 and 23.0% in 1983 to 1984. Among white women the corresponding percentages were 27.9%, 28.7%, 27.7% 27.7% and 25.9%. Among black men they were 39.3%, 38.9%, 39.3%, 38.4% and 37.2%. Only the black women did not show a lower percentage of smokers at the end than at the beginning of the five-year period, but the increase was minimal; their corresponding percentages were 34.1%, 36.5%, 33.3%, 35.8% and 34.2%.

Among white male smokers, the number smoking at least 20 cigarettes a day declined slightly over the five years, the successive annual age-adjusted percentages being 68.5%, 68.9%, 68.2%, 65.1% and 63.5%. White women showed no such change, the percentages being 56.0%, 56.3%, 57.8%, 53.4% and 56.1%, respectively. Black male smokers showed a slightly irregular decline as did white men; the respective percentages smoking at least 20 cigarettes per day were 48.4%, 48.6%, 48.9%, 43.7% and 44.5%. No clear trend was apparent in the black female smokers whose annual age-adjusted percentages of smoking at least 20 cigarettes a day were 34.9%, 34.7%, 38.3%, 38.6% and 33.8%.

The use of low-yield cigarettes showed some year-to-year variation but no clear time trends in any of the four race-sex groups.

In summary, there were some small downward five-year trends noted in the prevalence of cigarette smoking in white men and women and in black men and in the prevalence of heavy smoking among male smokers of both races. No increase in smokers' use of low-yield cigarettes was apparent.

Comparison With 1964 to 1968 Data

Smoking habits of MHC examinees were extensively studied during the 1964 to 1968 period.[2] The questionnaires used and methods of classifying smokers were different at that time. To approximate as closely as possible our present classi-

TABLE 2.—*Age-Adjusted Prevalence of Current Smoking by Sex and Race*

Sex	Race	Total Number, Age <80 Yr	Current Cigarette Smokers: Age-Adjusted Percentage*
Male	Asian†	4,511	23.0
	Black	9,598	37.9
	White	24,536	25.7
	Other and unknown	3,011	30.0
Female	Asian†	5,936	10.4
	Black	15,445	34.2
	White	28,236	27.6
	Other and unknown	3,846	25.8

*Adjusted by direct method with entire study population as standard; persons aged 80 years and over excluded.
†The Asians reported that they were in the following subgroups: Chinese descent, 44.9%; Filipino descent, 32.3%; Japanese descent, 13.4%; other Asian, 9.4%.

TABLE 3.—*Percentages of Cigarette Smokers Who Smoked 20 or More Cigarettes Per Day*

		Age, Years						
Sex	Race	15-19, %	20-29, %	30-39, %	40-49, %	50-59, %	60-69, %	70-79, %
Male	All	26.3	45.4	57.1	63.5	65.3	62.4	49.5
	Black	14.7	33.2	49.1	58.5	54.0	48.0	23.1
	White	37.0	57.7	66.1	70.7	75.5	70.3	55.1
Female	All	19.8	34.7	47.4	51.8	51.2	51.6	41.8
	Black	9.5	24.6	42.4	42.5	36.2	31.1	26.9
	White	32.6	47.2	54.6	62.1	61.6	58.4	44.8

TABLE 4.—*Percentages of Cigarette Smokers Who Inhaled at Least Part of the Time*

		Age, Years						
Sex	Race	15-19, %	20-29, %	30-39, %	40-49, %	50-59, %	60-69, %	70-79, %
Male	All	97.2	95.1	94.2	91.3	87.2	80.4	73.9
	Black	100.0	95.8	94.7	91.9	85.3	77.5	76.9
	White	96.7	96.7	96.5	94.1	90.5	84.5	77.8
Female	All	95.9	94.9	92.5	86.3	79.4	69.2	57.0
	Black	96.4	94.8	90.8	81.9	72.4	59.1	61.5
	White	97.7	96.3	95.1	92.6	85.2	73.7	57.1

TABLE 5.—*Percentages of Cigarette Smokers Who Smoked Low-Yield (<15 mg Tar) Cigarettes*

		Age, Years						
Sex	Race	15-19, %	20-29, %	30-39, %	40-49, %	50-59, %	60-69, %	70-79, %
Male	All	14.6	22.7	23.5	20.1	19.2	22.8	22.5
	Black	14.7	12.8	15.9	15.1	13.0	14.2	10.3
	White	16.3	30.7	29.6	24.6	24.0	26.4	25.9
Female	All	16.8	28.7	29.2	25.9	28.0	30.8	30.7
	Black	9.6	17.5	20.2	16.4	19.3	21.7	11.5
	White	22.5	40.9	37.2	33.7	34.6	34.2	33.5

TABLE 6.—*Percentage of Study Population Who Were Current Smokers and Percentage of Current Smokers Who Smoke at Least 1 Pack or 20 Cigarettes Per Day in the 1964 to 1968 (Oakland Only) Data Base and the 1979 to 1984 Data Base**

	% Current Smokers		% of Current Smokers Who Smoke at Least 20 Cigarettes Per Day	
	1964-1968	1979-1984	1964-1968	1979-1984
Males				
White	41.7	25.7	62.3	66.9
Black	51.6	37.9	40.0	47.9
Females				
White	38.9	27.6	49.5	56.1
Black	40.6	34.2	31.8	35.6

*All percentages are age-adjusted by the direct method to the same 1979 to 1984 standard. Persons with no or unknown response in the 1964 to 1968 data were excluded. Unknowns comprised less than 1% of the 1979 to 1984 data and were not excluded.

fication of current cigarette smokers, we looked at responses to the single 1964 to 1968 question, "During the past year did you smoke cigarettes?" We also looked only at persons examined then in Oakland because the vast majority of our combined 1979 to 1984 data was gathered in Oakland. There has been a sizable drop in the percentage of current smokers, both white and black and both male and female, over the (approximately) 15-year interval. Among smokers, however, the percentage who smoke at least one pack of cigarettes per day has increased (Table 6).

Discussion

Although not a representative sample of the San Francisco Bay Area population, our study group was large and heterogeneous and they were asked about smoking habits in a nonjudgmental health care setting; they were also comparable to a group whose smoking habits were assessed in detail during the 1964 to 1968 period.[2] Thus their reported habits are of interest to those who are concerned with recent trends and current smoking habits in this large US metropolitan area.

Overall, men showed only a slightly higher percentage of smokers than women and the male excess was present only in the age decades over 30 years. Of concern for the health of women in the future is the fact that under age 30, the percentage of female smokers recently exceeded that of men. In every age group, however, female smokers tended to smoke fewer cigarettes per day, and inhalation was less common in women, especially in the older age groups. Furthermore, women more often smoked low-yield cigarettes than men.

Racial differences in the prevalence of smokers were more striking than sex differences. Among the three largest racial groups, blacks showed the highest percentage of smokers, whites were second highest and Asians lowest with Asian women being substantially lower than other race-sex groups. The recent special public health efforts to decrease cigarette smoking among blacks, including a community-based project recently mounted by our department in Richmond, California, seem well justified by the racial differences here noted.

Interestingly, however, although more blacks smoke, blacks do not necessarily smoke more intensively than whites. We found that white smokers smoked more cigarettes per day on average and reported more inhaling of cigarette smoke than did black smokers. Blacks, however, were less apt to smoke low-yield cigarettes than whites.

As expected in a relatively health-conscious group receiving health examinations, our study group had a lower overall prevalence of cigarette smoking than the US population as a whole in 1980 and 1983[11,12]—about 5 to 10 percentage points lower in men and about 2 to 5 percentage points lower in women, depending on the age group considered. Our data, however, resemble national data with respect to male-female and black-white differences and to age trends in smoking habits. Nationally, men had a higher prevalence of smoking than women at all ages except 20 to 24 years, where women were slightly higher. Men smoked more cigarettes per day than women, and the heaviest smokers tended to be persons in the 40s and 50s. As in our study group, black men had the highest prevalence of smoking and white men had the second highest. Among women nationally (in 1980), there were only slight differences in smoking prevalence between blacks and whites, but by 1983 black women were nearly 10% more likely to be smokers than white women. In our study group, black women were nearly 25% more likely to be smokers than white women. Nationally as well as in our study population, both black men and black women were less likely to be heavy smokers than were white men and white women, respectively.

National data on the overall use of lower-yield cigarettes[13] were not readily comparable with our own. With respect to male-female and black-white differences and age trends, however, the 1979 to 1984 MHC population was similar to the US population in 1979[13]; low-yield cigarettes were used proportionately more often by women than by men and by whites than by blacks, but their use was not related to age. White men and white women were each about twice as likely to smoke low-yield cigarettes as black men and black women, respectively, both nationally and in our study group.

Although data from 1964 to 1968 and 1979 to 1984 were not strictly comparable, they are sufficiently similar to permit confidence that fewer of our MHC examinees smoked recently than during the earlier period, but that among the smokers, more are heavy smokers during the recent period. The latter is probably due to several causes, but one likely factor is that it is easier for those who smoke less to quit.[14] Thus, all of the health warnings concerning smoking that have been publicized since the 1964 Surgeon General's report seem to have had the greatest effect on those who smoke less. We did not collect cigarette yield data in 1964 to 1968, so the trend toward the use of low-yield cigarettes observed elsewhere cannot be evaluated in these data. Based on national sales data, however, the use of low-yield cigarettes was probably infrequent in the 1960s.[15]

During the five-year 1979 to 1984 period, changes in smoking habits were modest. There were small downward trends in the prevalence of cigarette smoking in men and white women and in the prevalence of heavy smoking among smoking men, but no overall reduction in the yield of the cigarettes smoked was apparent. The heavy marketing of low-yield cigarettes seems to have had little effect on our study group during the period.

National trends from the mid-1960s to the early 1980s in the prevalence and amount of smoking[11] are generally similar to those found in our population of MHC examinees: the prevalence of smoking declined, but smokers tended to smoke more cigarettes per day. The declines in smoking prevalence nationally were greater among men than women, slightly greater among white men than among black men and much greater among white women than among black women. Smoking declined most among white men and least among black women both nationally and in the MHC population. Between 1980 and 1983 nationally (for all races combined), declines in heavy smoking were greater among women than among men. In contrast, our study group showed a slight decline among men but not among women between 1979 and 1984. This inconsistency could reflect differences in the definition of heavy smoking (20 or more cigarettes per day in our study versus 25 or more in the national data) or in the time periods considered.

In conclusion, our data indicate some favorable trends in smoking habits since the mid-1960s, particularly a decrease in the proportion of examinees who smoke cigarettes. Not all

indices of smoking intensity declined, however, and even in this relatively health-conscious population in recent years, slightly more than a fourth of persons were current cigarette smokers. Thus, from a public health point of view, much still needs to be done to discourage smoking. Of particular concern are blacks, more of whom smoke than of other racial groups, young women, who have overtaken young men in smoking prevalence, and the tendency of smokers to smoke more cigarettes, on average, in recent years than in the mid-1960s.

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Plasma Ferritin Determination as a Diagnostic Tool

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Plasma ferritin is a secretory component of intracellular ferritin synthesis. In normal persons its amount reflects the size of iron stores. A decrease to less than 12 μg per liter indicates iron deficiency. Increased iron stores are associated with an increased plasma ferritin level. Various other conditions, however, can increase the plasma ferritin concentration including increased metabolism, inflammation, tissue damage and neoplastic disease. The use of the plasma ferritin determination in diagnosing iron overload depends on excluding these other causes, leaving storage iron as the only explanation for the increased plasma ferritin. It is then necessary to establish the parenchymal nature of the iron overload by showing an elevated transferrin saturation and, if elevated, the more definitive liver biopsy should be done.

(Finch CA, Bellotti V, Stray S, et al: Plasma ferritin determination as a diagnostic tool. West J Med 1986 Nov; 145:657-663)

Determining plasma ferritin levels has provided clinicians with a convenient means of assessing iron balance. The measurement has been used extensively to evaluate body iron stores, particularly in the detection of iron deficiency and iron overload. It has largely replaced bone marrow iron examination in separating the anemia of inflammation from that of iron deficiency. As is true of any method, there are limitations in its clinical application, relating to pathologic states that affect the plasma ferritin concentration and complicate its interpretation. In the present review we have provided a physiologic background for interpreting plasma ferritin levels and have discussed its clinical usefulness and limitations. For a more comprehensive discussion of this topic, the reader is referred to the excellent review by Worwood.[1]

Normal Physiology

Ferritin is the iron storage molecule of the body (Figure 1). The protein has a molecular weight of about 460,000 and comprises 24 subunits, a mixture of H and L polypeptides that together form a hollow sphere capable of holding iron.[2] Intracellular iron passes through the portals of this protein shell and is deposited as aggregates of ferric hydroxide phosphate that may amount to as much as 25% of the protein by weight. This intracellular iron-storing ferritin is synthesized by the smooth endoplasmic reticulum of the cell (Figure 2). Initially free in the cell sap, it may later be found within lysosomal membranes where it is compacted into semicrystalline form. Still later, it may be converted by lysosomal action to a denatured mass of insoluble hemosiderin. Ferritin free in the cytoplasm has a life span of a few days, whereas the turnover of hemosiderin aggregates is thought to be slower. The amount of intracellular ferritin synthesized each day is that required to replace catabolized ferritin and hemosiderin and to accommodate any additional iron entering the cell.

Normal plasma ferritin is believed to be synthesized by the rough endoplasmic reticulum and is for the most part glycosylated before being secreted from the cell, presumably by the Golgi apparatus.[3] Plasma ferritin also differs from cellular ferritin in having a very low iron content. There appears to be a correlation between the internal (iron storage) pathway and the much smaller external (secretory) pathway, so that the plasma ferritin concentration reflects the amount of ferritin within body cells.

Storage iron is located predominantly in reticuloendothe-

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lial cells and hepatocytes.[4] These cell types are the major contributors to the plasma ferritin pool. The reticuloendothelial component may be identified by the increase in plasma ferritin that follows phagocytosis of nonviable erythrocytes (Figure 3). Less direct evidence of the contribution of hepatocytes is seen in the relation between plasma ferritin and hepatocyte iron stores in idiopathic hemochromatosis (Figure 4). Patients in the early stage of the disorder have an increased amount of hepatic ferritin but a normal amount and turnover of reticuloendothelial iron,[5] so that the elevated level must relate to the hepatocyte iron overload. Furthermore, we have found the plasma ferritin in these early-stage patients to show the same proportion of glycosylation as is found in serum ferritin of a normal subject—that is, about 70%. We conclude that hepatocytes, the reticuloendothelial cells and presumably all other body cells synthesizing ferritin secrete a representative proportion into the plasma. Determining the plasma ferritin level provides a more general assessment of iron stores than does marrow aspiration, which involves the examination of reticuloendothelial cells in the marrow for hemosiderin.

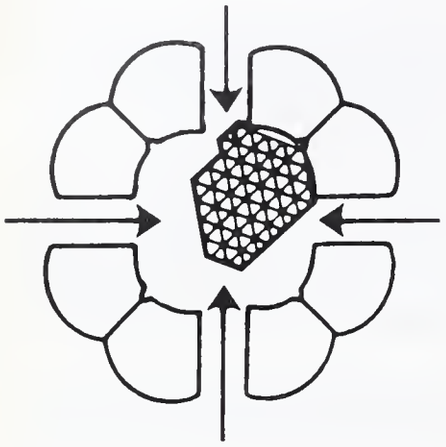

Figure 1.—A diagrammatic portrayal of the protein shell and internal iron core of the tissue ferritin molecule. Portals of entry for iron are indicated by arrows.

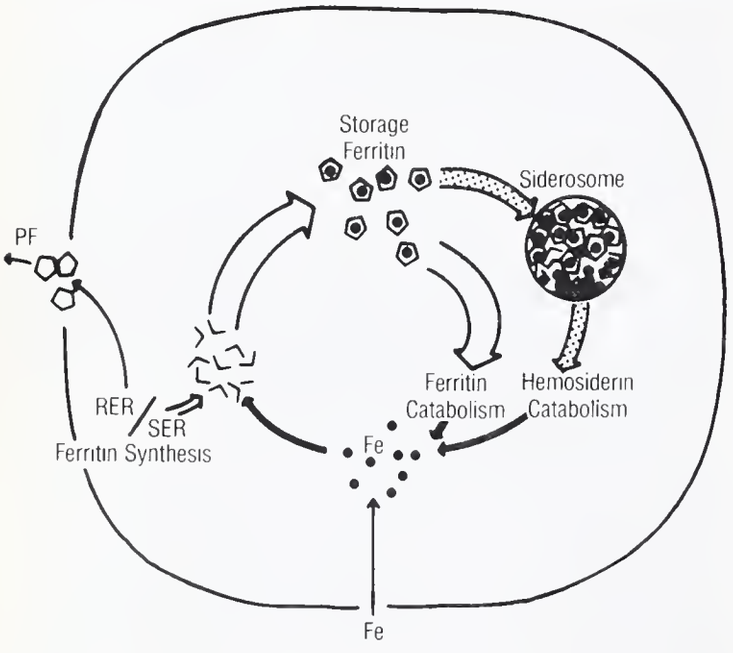

Figure 2.—Intracellular ferritin metabolism is summarized. The smooth endoplasmic reticulum **(SER)** synthesizes polypeptide components of the apoferritin molecule in response to the presence of iron **(Fe)** derived either from ferritin catabolism or from iron entering the cell. A small fraction of apoferritin is synthesized by rough endoplasmic reticulum **(RER)** and is excreted from the cell. This fraction is recognized as plasma ferritin **(PF)**. Within the cell some ferritin molecules undergo catabolism within a few days, liberating their iron. Other iron is derived from the slower turnover of hemosiderin and from iron entering the cell.

Methods

While it had been appreciated for some time that small amounts of ferritin might be present in the circulation in

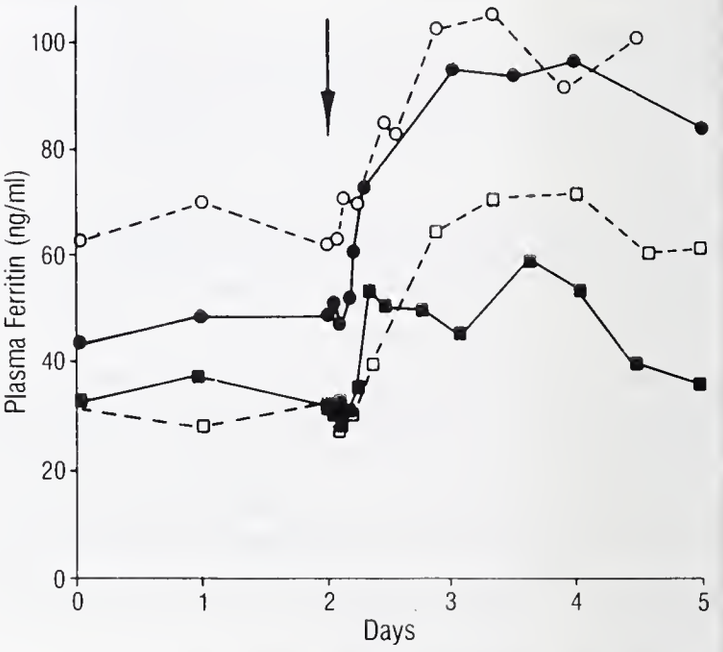

Figure 3.—Increased plasma ferritin levels following iron loading of reticuloendothelial cells. In this figure is shown the effect on the plasma ferritin concentration of 25 to 50 ml of nonviable erythrocytes injected intravenously on day 2 **(arrow)**. The plasma ferritin concentration increased 20 to 40 μg per liter within 24 hours.

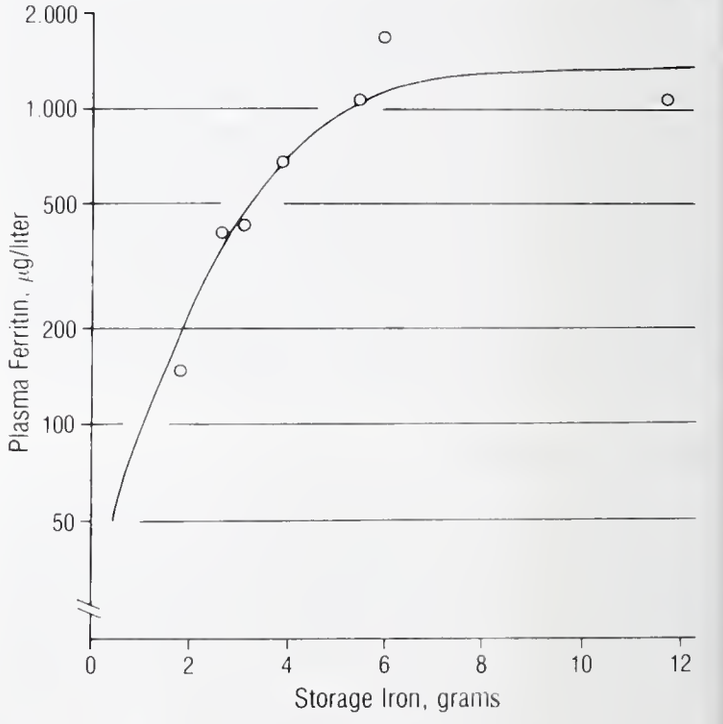

Figure 4.—Relation between plasma ferritin concentration and hepatocyte iron stores in patients with early idiopathic hemochromatosis. These patients had normal liver morphology except for excessive parenchymal iron stores. The amount of storage iron was determined by phlebotomy.

certain pathologic states, the exceedingly small amounts of circulating ferritin made quantitation difficult. Only with the development of immunologic techniques could it be shown that ferritin was present in the plasma of healthy persons.[6] Various procedures have been developed, usually using liver ferritin as an antigen to produce an isotopically labelled or enzyme-linked antibody against ferritin.[7,8] The essential features are that the background of the method is not so great as to interfere with accuracy at low levels and that proper dilutions are made when elevated levels are encountered so that the magnitude of increase can be accurately determined. The "hook" effect whereby high levels of ferritin are not recognized due to a prozone phenomenon is no longer seen with the use of better antibodies. A geometric mean is usually used to express normality because of the log distribution of values in healthy persons.

Interpreting Normal Values

It was apparent from the first that differences in serum ferritin concentration of healthy persons were due primarily to variations in iron stores. For example, mean values for menstruating women of about 30 μg per liter and for men of about 100 μg per liter correspond to their anticipated mean iron stores of 300 and 1,000 mg, respectively. More direct evidence was provided by the correlation observed between plasma ferritin and the amount of storage iron that could be removed from normal subjects by phlebotomy.[9] Other relationships supported the same hypothesis. The amount of marrow hemosiderin and the liver iron content correlated with the plasma ferritin concentration.[10,11] Iron absorption that is inversely proportional to iron stores showed a similar relationship to serum ferritin concentration in healthy persons.[12] It was postulated that 1 μg per liter of serum ferritin corresponded to 8 to 10 mg of storage iron.[1,13] While this expression is a workable one in normal adults, it does not take into consideration differences in body size, particularly relevant in characterizing iron stores in infants. It is suggested that when dealing with children or small adults, 1 μg per liter of plasma ferritin is better considered equivalent to 120 μg of storage iron per kilogram of body weight.

Changes in plasma ferritin through life mirror the state of iron balance (Figure 5).[1] In newborns, the geometric mean is about 125 μg per liter, increasing during the next three or four weeks to a maximum of about 250 μg per liter as erythrocytic iron shifts to stores. Thereafter the plasma ferritin concentration decreases through infancy to 10 to 20 μg per liter as iron stores are mobilized to provide for the increase in erythrocytic mass. This low plasma ferritin level continues during early childhood but increases to 20 to 30 μg per liter during late childhood and adolescence. At these ferritin concentrations, it may be difficult to see marrow hemosiderin because it is present in limited amounts and because its visualization depends on having adequate amounts of marrow stroma for examination.

An appreciable increase in plasma ferritin occurs in men between the ages of 15 and 30 years, reflecting a more favorable iron balance once growth has ceased.[14] Thereafter a more gradual increase occurs into old age.[15] In an adult menstruating woman, the level remains at about 30 μg per liter[14] until after menopause when there is an increase, ultimately reaching or nearly reaching the corresponding value for men. It is difficult to say whether increases in old age reflect only a more positive iron balance or are also the result of inflammatory processes, but probably both contribute.[16,17] In the first trimester of pregnancy, a value somewhat above that of the nongravid state is found.[18] Later this falls to values below 20 μg per liter in pregnant women who are not taking supplemental iron.[19,20]

Plasma ferritin concentrations in healthy persons of the same age and sex will vary widely. For example, in men values range from 30 to 300 and in women from 10 to 200 μg per liter. These differences are considered to be due chiefly to differences in iron balance—that is, to the variety of causes that can affect iron absorption or iron loss. There are no diurnal variations in plasma ferritin levels, but there are individual physiologic variations from day to day or week to week that result in a coefficient of variation of about 20%.[21] The cause of these changes is not known but presumably reflects fluctuations in intracellular protein synthesis or leakage of intracellular storage ferritin, or both. Because starvation, heavy exercise[22] and inflammation[1] are known to influence the ferritin level, one might guess that subclinical effects of a similar nature might be involved.

Interpreting a Low Plasma Ferritin Level

One of the principal uses of the plasma ferritin level is in identifying a case of iron deficiency. The development of iron deficiency first involves a reduction in the amount of tissue ferritin and hemosiderin (store depletion), then exhaustion of stores with a decrease in plasma iron supply (iron-deficient erythropoiesis without anemia as defined by laboratory criteria) and, finally, a recognizable reduction in erythrocyte mass (iron deficiency anemia).[23] Stores are considered to be exhausted if the plasma ferritin concentration is less than 12 μg per liter. The measurement of plasma ferritin has provided an alternative to the direct examination of marrow iron stores, permitting detection of the earliest stage of iron deficiency. In the more advanced stages of iron deficiency where anemia of some severity is present, all other types of anemia than iron deficiency would elevate the ferritin level above normal due to the shift of erythrocyte iron to tissues.

Other than its convenience and noninvasive nature,

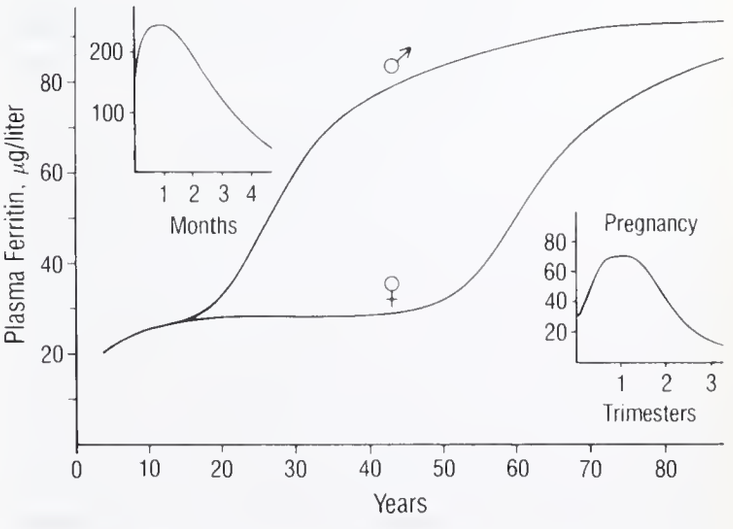

Figure 5.—Mean ferritin concentration as a function of age. The insert on the left indicates the changes in ferritin concentration during the first few months of life and the insert on the right, changes during pregnancy trimesters.

plasma ferritin determination has an advantage for clinicians over other measurements of iron deficiency in two situations. The first is in detecting a negative iron balance, for example, where there is occult bleeding but the tissue iron supply is still sufficient to prevent anemia. The significance of a low ferritin concentration depends on the age and sex of a person and on the severity of the anemia. A ferritin value of 15 μg per liter in a man even without anemia suggests pathologic iron depletion, usually on the basis of blood loss. On the other hand, in the latter half of infancy, in pregnancy and in women with heavy menstruation, a plasma ferritin level of 15 μg per liter in the absence of anemia is to be expected.

The measurement of plasma ferritin levels is of particular value in monitoring conditions in which iron deficiency frequently develops. For example, patients with renal failure who are receiving dialysis treatment are often in negative iron balance due to blood removal for laboratory tests and blood left behind in the dialysis machine. Serial measurements of serum ferritin levels allow one to anticipate iron deficiency before anemia appears.[24-26] Other cases in which iron balance is in jeopardy include patients with malabsorption of dietary iron after gastric operations,[27] women with intrauterine devices that increase menstrual blood loss[28] and patients with blood loss who have been given iron parenterally but who may be expected to become iron deficient again because of continued bleeding.[29] The measurement of plasma ferritin levels may well find its most important use in defining the capacity of blood donors to give blood.[30,31]

The second special use of the plasma ferritin measurement in patients with iron deficiency anemia is in distinguishing that from the anemia of inflammation. In both conditions there is a deficient iron supply, reflected in a transferrin saturation of less than 16% and an elevated erythrocyte protoporphyrin level. Often it had been necessary to examine the marrow aspirate for hemosiderin, absent in cases of iron deficiency and normal to increased with inflammation. Ferritin determination has replaced marrow aspiration for this purpose because it not only detects the presence of iron stores but also ferritin levels are disproportionately elevated in the presence of inflammation. Studies of patients with inflammatory bowel disease,[32] with rheumatoid arthritis[33] and with renal failure[34] suggest that in the presence of inflammation, a serum ferritin level of below 50 to 60 μg per liter will identify those persons who will respond to iron therapy. The hemoglobin of those with higher values will not respond.

Iron by mouth in the usual therapeutic dose for one to two weeks has virtually no effect on plasma ferritin concentrations in a normal subject, nor does it affect the plasma ferritin level in persons with iron deficiency unless treatment is continued several months after the anemia has been corrected.[35] Parenteral administration of iron does increase the plasma ferritin concentration, the initial increase being excessive for the stores produced.[36]

There are only two conditions other than iron deficiency recognized as lowering plasma ferritin levels. Hypothyroidism, presumably by retarding protein turnover, will reduce the amount of plasma ferritin produced. Ascorbate deficiency interferes with ferritin synthesis in a more specific manner.[37] While it is possible that a misleadingly low ferritin value may be found in a patient with one of these conditions, this has not been recognized as a problem clinically. A more likely possibility is that iron deficiency may be missed because of some complicating disease that results in an increase in plasma ferritin.

Interpreting a High Plasma Ferritin Level

There are a variety of causes of an elevated plasma ferritin level other than an increase in iron stores per se. Indeed, most elevated values are due to complicating diseases. The most common cause is inflammation. In such cases, iron stores are usually increased due to the shift of erythrocyte iron to tissues. Ferritin concentration, however, is increased disproportionate to stores, suggesting an additional effect on ferritin turnover (Figure 6). The proportion of glycosylated plasma ferritin is unchanged, indicating that the normal mechanisms for ferritin production are operative.[38]

An increased ferritin concentration may be the result of an increase in the synthetic rate as part of the general increase in cellular metabolism. Patients with hyperthyroidism have mean values several times those consistent with their body iron stores, plasma ferritin values ranging as high as 1,000 μg per liter in men and 300 μg per liter in women.[39] There is also an increase in plasma ferritin levels during the first trimester of pregnancy as noted earlier, but the cause of this, whether due to an increased metabolism or an inflammatory-like state, is unclear.

Plasma ferritin levels may be greatly increased by damage to ferritin-rich tissues, in which case most of the ferritin is nonglycosylated and contains iron. Liver disease is the most frequent offender,[40] but damage to other ferritin-rich tissues may be responsible. Such massive release of tissue protein may be misleading if laboratory data are incorrectly interpreted. A case in point was that of an elderly woman suffering from cardiopathy who was found to have a plasma ferritin value of greater than 20,000 μg per liter, whereas her plasma iron level was reported as 758 μg per dl and total iron binding capacity 970 μg per dl. The presence of an unsaturated iron binding capacity of more than 200 μg per dl excluded iron overload as a cause of her high ferritin level. The alternate explanations were either prior administration of iron dextran (which was not the case) or iron-containing ferritin released

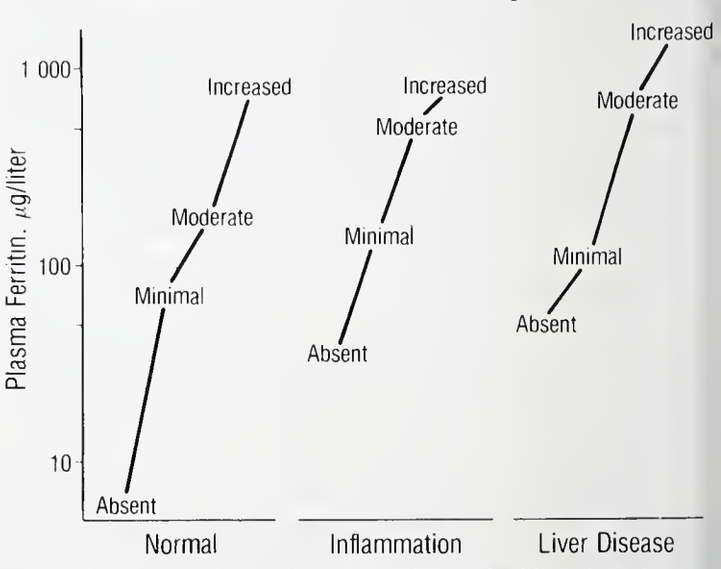

Figure 6.—Comparison of average plasma ferritin values for four grades of marrow hemosiderin in normal subjects, in patients with inflammation and in those with liver disease. For any given grade of marrow iron, the plasma ferritin level is higher in the two disease states (from Lipschitz et al[13]).

from damaged tissues. Levels of plasma iron and ferritin subsequently fell towards normal. At necropsy two weeks later, she had no tissue iron overload but an organizing splenic infarct.

Another mechanism for increased ferritin is its production by malignant tissue.[41] While inflammation and tissue necrosis are important causes of an elevated ferritin level in many patients with neoplastic disease, the presence of more acidic plasma isoferritins in some instances suggests that certain neoplastic cells can elaborate their own ferritin.[42] Such isoferritins can be identified by specific antibodies, but the practical usefulness of differential determinations of isoferritins at the present time is questionable.[43,44] Using the standard ferritin method, mean values in adult patients with acute myeloid leukemia have been reported to be about 1,500 μg per liter with a range from 400 to 4,000.[45] Other hematologic malignant disorders and solid tumors involving breast,[44,46] liver,[47] pancreas[48] and cervix[49] may also show levels in the thousands. In general, the elevation is proportionate to the amount of neoplastic tissue and extent of metastasis.[50] Levels return toward or to normal with successful therapy.[41,51,52]

Diagnosing Iron Overload

An elevated plasma ferritin level is reason for considering the possibility of iron overload, but with certain qualifications. In the early stages of iron loading, measuring the plasma ferritin level is of limited value because of the much greater frequency with which other factors such as inflammation confound its interpretation. Most patients with ferritin concentrations between 200 and 2,000 μg per liter will have normal or depressed transferrin saturations, and their elevated values will be most often due to inflammation or tissue damage.[53] A more important screening test is finding an increased transferrin saturation. While plasma ferritin levels may be increased by iron in either reticuloendothelial or parenchymal cells, a sustained increase in transferrin saturation of more than 70% is a prerequisite for parenchymal loading.

The most frequent parenchymal iron loading state and the most difficult to diagnose is idiopathic hemochromatosis. Persons homozygous for the hemochromatosis gene accumulate excess iron for many years with no clinical manifestations. Their early detection depends on population screening, a chance measurement of the iron state for some other cause or specific testing because of a diagnosis of idiopathic hemochromatosis in a family member or, rarely, the detection of increased liver density by computed tomographic scan or magnetic resonance imaging. The earliest detectable abnormality is an increase in transferrin saturation.[54] Plasma ferritin concentration will increase above normal after about 20 years of age, reflecting the growing iron stores. Even in persons older than 40 years, serum ferritin values of less than 500 μg per liter are unlikely to represent significant overload. Our experience has been that 5 grams or more of storage iron will elevate the plasma ferritin concentration to about 1,000 μg per liter (Figure 4). In seven patients with early parenchymal overload but no evidence of liver cell damage by biopsy examination, the mean relationship between tissue iron levels in milligrams as measured by phlebotomy and plasma ferritin levels in micrograms per liter was found to be 8:1. Transferrin saturation in all exceeded 70% (normal 30 ± 10%).

The most difficult distinction lies between primary iron overload with hepatic damage and parenchymal liver disease with increased storage iron because in both conditions plasma ferritin levels and transferrin saturation will be elevated.[55,56] The only test of liver function in cases of early idiopathic hemochromatosis that is apt to show mild elevation is the alanine aminotransferase.[57] In general, liver function test results are more abnormal with primary liver disease. The deferoxamine iron excretion test is not positive in patients with idiopathic hemochromatosis in the absence of hepatic fibrosis, 24-hour values being less than 3 mg in our experience. In these cases a liver biopsy is most helpful. The loading of all hepatocytes without deposits of Kupffer's cells and without evidence of tissue damage is nearly pathognomonic of idiopathic hemochromatosis. A disproportionate amount of liver iron is to be expected in early hemochromatosis because stores are located selectively in hepatocytes.[5] Identifying other family members with iron excess will confirm the diagnosis.

In a patient in an advanced stage of liver disease with associated iron overload, laboratory tests and even liver biopsy may be of little help in determining the cause of the disorder.[58] Transferrin saturations greater than 80% are found in both idiopathic hemochromatosis and with liver damage due to other causes. Distinguishing features for primary liver disease are more abnormal results of liver function tests and a greater degree of portal fibrosis and portal vein obstruction in relation to the amount of iron present.[58,59] The lesser amount of iron with primary liver disease is usually reflected in a ferritin concentration between 500 and 2,000 μg per liter, whereas in patients with advanced idiopathic hemochromatosis, values are usually between 2,000 and 8,000 μg per liter.[59] In the presence of cirrhosis, the deferoxamine test is also of some help in showing the greater iron load, the 24-hour urinary iron content after administration of 0.5 grams of deferoxamine usually being less than 3 mg of iron in primary liver disease and more than 4 mg in cases of idiopathic hemochromatosis.[58] The amount of liver iron is more precisely assessed by histologic examination or chemical analysis. Still more conclusive for diagnosing idiopathic hemochromatosis is finding iron overload in another sibling.

It is desirable to remove excess parenchymal iron by phlebotomy whenever it can be done. Ferritin values in an untreated patient with idiopathic hemochromatosis may fluctuate from week to week, obscuring the early effects of iron removal. The fall in ferritin level, however, is greater per milligram of erythrocyte iron removed at higher levels and progressively decreases as the ferritin concentration approaches normal values (Figure 7). Only at concentrations below 1,000 μg per liter can plasma ferritin levels be used to evaluate the size of residual iron stores and to predict the number of phlebotomies that will be required to return stores to normal.[60] Once the ferritin concentration is below 100 μg per liter, it is usually sufficient to monitor the state of iron balance by an annual plasma ferritin determination. The number of phlebotomies thereafter, usually three to four per year, can be adjusted so as to keep the ferritin level below 100 μg per liter. Determining the transferrin saturation is not useful in monitoring the subsequent iron state, as values fluctuate widely even when iron stores have been returned to normal, reflecting daily iron absorption more than overall iron balance.

Parenchymal iron overload is also likely to develop in patients with thalassemia, sideroblastic anemia, refractory anemia with hyperplastic marrow and occasionally patients with hemolytic anemia.[3,61,62] The plasma ferritin level will characterize iron stores in such patients. In the absence of the other causes discussed and if associated with an elevated transferrin saturation, a value of more than 1,000 μg per liter is cause for concern. If a patient has been repeatedly transfused, an elevated ferritin level may be expected,[13] but iron may be largely in reticuloendothelial cells. This is true particularly in patients with aplastic anemia in whom marrow aplasia results in an elevation of transferrin saturation and transfusions will progressively elevate the plasma ferritin concentration. The hazard of parenchymal damage in general is much greater in those patients with anemia who have hyperplastic erythroid marrow.[4]

Inconsistencies

There have been reports of apparent inconsistencies between plasma ferritin levels and other measurements of storage iron. The augmentation of plasma ferritin in patients with inflammation, in hypermetabolic states, with tissue damage and with neoplastic disease has been previously discussed. Other reports suggest that problems occasionally occur even in the absence of such conditions. Plasma ferritin levels often appear too high in cases of sickle cell disease when compared with marrow iron stores, presumably due to the more widespread deposits in the reticuloendothelial system in this disease.[63] Pronounced increases in ferritin values have occurred without corresponding increases in iron stores in patients with lysinuric protein intolerance[64] and in those with Gaucher's disease.[65] The plasma ferritin concentration has been less than expected from the liver iron content in some patients with thalassemia.[66] This may be at least in part related to ascorbate depletion.[67] Low ferritin concentrations have been reported in persons with congenital anemia (HEMPAS [hereditary erythroblastic multinuclearity associated with positive acidified serum]) in the presence of iron overload.[68] The report of a unique family with increased iron stores and cirrhosis in the presence of near-normal plasma ferritin concentrations indicates that the plasma ferritin level is not infallible as a predictor of iron overload.[69] The reason for these inconsistencies is not apparent, but they rarely occur.

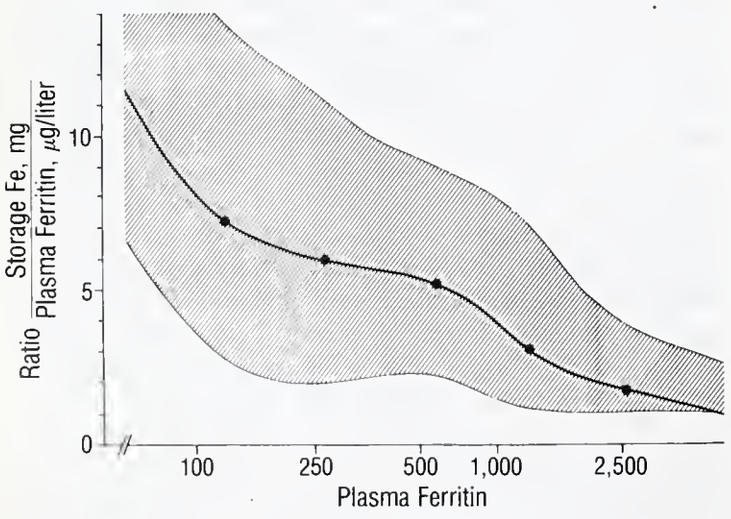

Figure 7.—Relationship between the amount of iron removed at phlebotomy and changes in ferritin concentration in 15 patients with idiopathic hemochromatosis. The shaded area represents the range of values observed. The ratio of iron to plasma ferritin progressively increases as iron stores are reduced. Between levels of about 1,000 and 100, however, there was a rather constant relationship at about 7 mg storage iron to 1 μg per liter of plasma ferritin.

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The Artificial Heart—Progress, Problems, Prognosis

Discussant
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This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of Washington School of Medicine, Seattle. Taken from a transcription, it has been edited by Drs Paul G. Ramsey, Associate Professor of Medicine, and Philip J. Fialkow, Professor and Chair of the Department of Medicine.

ROBERT L. VAN CITTERS, MD:* Heart disease is responsible for about 50% of all deaths in the United States. About a third of these deaths occur before the age of 65, some before age 35. Many of these early deaths occur in people without coexisting disease. The concept of an artificial heart arose from the belief that many early deaths could be postponed and the useful period of many lives extended if it were possible to replace the diseased heart with a prosthetic device.

Work had been under way toward developing such a device in a few laboratories as far back as the 1930s, but congressional identification of mechanical circulatory support as a priority area within the National Institutes of Health (NIH) in 1963 provided impetus for the subsequent development of the Artificial Heart Program of the National Heart, Lung and Blood Institute. Studies at that time projected that as many as 130,000 people annually might benefit from an artificial heart and that it was reasonable to anticipate the development of a device with acceptable operating characteristics within five years. More than 20 years and $200 million later, very substantial progress has been made toward that goal, but it will be at least five more years before a totally implantable device is available for clinical use.

Recent clinical trials in the private sector using a tethered, pneumatically actuated device have focused substantial controversy not only on that effort, but also on the Artificial Heart Program of the NIH and on the concept itself. It will be the purpose of this presentation to review some aspects of the historical development of the Artificial Heart Program of the NIH, to present a nontechnical description of its current status and to examine some of the questions that potential availability of an artificial heart has raised.

The concept of replacing natural organs with mechanical prostheses or of supplementing their function with assist devices was known and practiced in antiquity. Greek sculptures dating back to the fourth century BC depict persons with prosthetic limbs; 15th-century woodcuts show monks wearing spectacles as they peruse ancient manuscripts, and many well-known figures throughout history are known to have used dental prostheses. These and other early prosthetic devices shared several characteristics; all were external, inert, nonpowered and would in today's parlance be classified as "low-tech" devices. Further, their evolution was slow: wooden legs changed very little over many centuries, 15th-century spectacles differ only in style from those in use today and false teeth are still just that.

A fundamental change took place following World War II. Rapid advances in technology, the development of new biomaterials and an enhanced understanding of basic biologic processes led to the development and widespread use of a broad variety of new devices—lens implants, artificial joints, prosthetic vessels and valves. New technologies such as renal dialysis provided an assist for organ functions and advances in immunology, and newly developed surgical techniques led to the establishment of successful programs for cornea, kidney, heart and marrow transplantation.

Committing a serious effort to replace the heart with a mechanical device has been a relatively recent development. Several factors have contributed. A large share of our current knowledge of the function and control of the circulation has emerged recently. Important advances have been made also in the understanding of basic biologic processes, such as clotting mechanisms, and there has been a substantial enhancement in technical capability, such as the development of new materials and the application of electronics.

Despite deep-seated philosophic, religious and emotional connotations, the heart is, for practical purposes, primarily a pump—an organ whose fundamental function is a mechanical one. Technology today has a far greater capacity to replace body structures and functions that are mechanical than those

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ABBREVIATIONS USED IN TEXT

LVAD = left ventricular-assist device
NIH = National Institutes of Health

that are biochemical or neurohumoral. It is now technically possible to build excellent mechanical pumps, and the heart is a suitable candidate for replacement by a prosthetic device.

Historical Highlights in Artificial Heart Development

The first account in which experimental attempts were made to replace the heart's function in animals with a mechanical device was published by Gallois in 1812.[1] Gallois theorized,

> If one could substitute for the heart a kind of injection—of arterial blood, either natural or artificially made—one would succeed easily in maintaining alive indefinitely any part of the body whatsoever.

Over the next century several investigators reported intermittent progress toward developing techniques and apparatuses for perfusing organs.[2] The modern era of mechanical circulatory devices began, however, with the work of Gibbon and others on extracorporeal circulation in the 1930s, culminating in 1939 with Gibbon's seminal contribution of a heart-lung pump with a practical oxygenator.[3] Much of this work came to a standstill during World War II, but in the immediate postwar period the development of cardiac catheterization greatly enhanced the ability of physicians to diagnose congenital and valvular heart diseases and to plan new approaches for their management. Other advances, such as improvements in anesthesia, helped to broaden the range of cardiac conditions amenable to surgical treatment and provided impetus for further refinement of heart-lung pumps. In 1952 a mechanical device was first used to bypass the function of the left ventricle in a human patient during repair of a mitral valve,[4] and later in the same year the heart was totally bypassed with the use of a mechanical heart-lung pump during repair of an atrial-septal defect.[5] Thus, by 1952 mechanical replacement of the heart had taken place.

During the next decade several improvements were made and many new heart-lung pumps evolved. As replacements for the heart, however, all such devices had serious limitations; because of their great size they were necessarily external, and it soon became apparent that there was an inverse relationship between pump time and survival. Nevertheless, the development of these heart-lung pumps for use in the surgery set the stage for the development of an entirely implantable artificial heart.

In 1963 Congress appropriated $581,000 to the National Institutes of Health for the specific purpose of developing an artificial heart. At least in part, this targeted approach seems to have stemmed from the success of several other government agencies in directing high-priority research projects, such as the Manhattan Project or the space program. The Artificial Heart Program that emerged was among the first congressionally mandated programs at NIH and was, in turn, the National Heart Institute's first targeted research effort. A systems approach was adopted. The potential need for such a device was analyzed, estimates were made of its costs and benefits and a plan was adopted that called for an orderly approach to major technical programs and for development of a family of devices—emergency devices, temporary devices, short- and long-term assist devices and total replacement devices. To take advantage of expertise in industry, the standard NIH approach of investigator-initiated research was supplemented by research contracts with individual researchers, universities and commercial organizations. During the next several years, progress was made in developing instrumentation, evaluating the biocompatibility of materials and designing and testing components and prototypes. The initial goal of a completely implantable mechanical replacement by 1970, however, proved to be unrealistic.

Consequently, the focus of the program was shifted from a completely artificial heart to the staged development of a family of devices with the intermediate aim of developing a left ventricular-assist device (LVAD)—that is, a completely implanted pump with a single pumping chamber that could assist a failing ventricle by pumping blood from the left ventricle into the aorta. Work on a nuclear power source was terminated, and pneumatically activated devices were not pursued because these required tethering the patient to a large external console by tubes that passed through the chest wall to transmit power. Emphasis was placed on electrical and thermal engines. Strategies were implemented for an orderly sequence of bench and animal testing so that mechanical performance and physiologic effects could be validated in the long term before clinical investigation was initiated.

It has been the intent of the Artificial Heart Program to establish completely the efficacy of the LVAD as a preliminary step to proceeding with work on a totally implantable cardiac replacement system. This reflects decisions made early in the program that the assist device have fewer components and fewer sources of failure, that technologic problems are avoided by matching the performance of two pumps, that solutions to problems for the assist device can be applied to the total cardiac replacement system and that failure of the device would not result in immediate death. The immediate goal is to develop an electrically powered, fully implantable assist device with a two-year reliability (Figure 1). An electrical pump would remove blood from the left ventricle and return it to the descending aorta. The primary energy source is a rechargeable external battery pack, shown in Figure 1, to be worn as a belt. This set of batteries would require charging from a standard wall current every eight to ten hours. In addition, energy would be transmitted via electromagnetic coupling from an external coil, worn like a belt, to an implanted secondary coil connected to a small, implanted, rechargeable battery. This would provide power for 30 to 45 minutes of pump operation, during which time the patient could be free of any external connections. Implanted components of these assist devices weigh about 1,200 grams and occupy about 1,000 cc; the external battery pack weighs about 3,000 grams. Currently four completely implantable, electrically powered, left ventricular-assist systems are undergoing reliability tests on the bench and in animals. The immediate goal is to establish that a totally implantable assist system will meet a rigorous set of performance criteria defined in the device-readiness test program with two-year reliability.[6] The major performance criteria are listed in Table 1. It is anticipated that these tests will be completed in 1986 and one or more of these devices will become available for clinical

investigative use in 1987. A more distant goal is to create a device that would permit five years of reliable operation.

Development of an implantable, total heart replacement will follow the sequence established for assist devices—that is, validation through bench and animal testing, followed by clinical evaluation. As shown in Figure 2, the implanted, fully artificial heart would replace a diseased heart—that is, the natural heart would be removed and the inflow-outflow channels of the implanted device would connect with anatomically appropriate vessels. The entire heart is about 50% larger and heavier than the assist device. A thermal power system is currently under development that offers a potential for smaller size and weight and longer operation.

Why an Artificial Heart?

The rationale for developing an artificial heart relates to the perceived need. Subsequent study groups, however, have revised downward the estimate of 130,000 patients who might benefit each year from such a device. Estimates of the need must take into account such factors as subsequent medical and surgical progress, the effectiveness of new therapies, the decline in coronary heart disease and the recent awareness of prevention. They will differ from estimates of demand and will involve factors such as effectiveness of the device, quality of life and cost. For these reasons, and because clinical criteria have not yet been defined, it is not possible to come up with precise numerical estimates of actual usage.

A population-based study, however, was recently used to estimate the order of magnitude of the number of eligible candidates (D.G. Pesche, R.L. Frye, D.C. McGoon, et al: "Selection Criteria and Estimated Number of Candidates for the Total Artificial Heart in the Population of Olmsted County, Minnesota," unpublished data, May 1984). Charts of all patients within a defined population who had died during a five-year period were examined by a panel that used a precisely defined set of criteria to assess whether each patient might have been considered a candidate for management with an artificial heart. Only those patients between ages 15 and 69 years who had severe, irreversible depression of left ventric-

TABLE 1.—*Summary of Performance Goals Defined by Device Readiness Program for Current Generation of Left Ventricular Assist Systems*

Goal	*Unit*
Cardiac output	up to 10 liters/min
Heart rate	120/min
Blood pressure, systolic	120 mm of mercury
Filling pressure	0-15 mm of mercury
Simple control system	
At least 2 years reliable implanted operation	
No hemolysis, clot, emboli	
Compatible with body (nontoxic, noncorrosible and so forth)	
Impervious to body fluids, no leakage	
Operates at body temperature	
Rechargeable external energy supply	10 hours
Rechargeable internal energy supply	30 min
Operates in any orientation or environment	
Shape, weight, volume compatible with anatomy	
Psychologically acceptable level of noise, vibration and so forth	

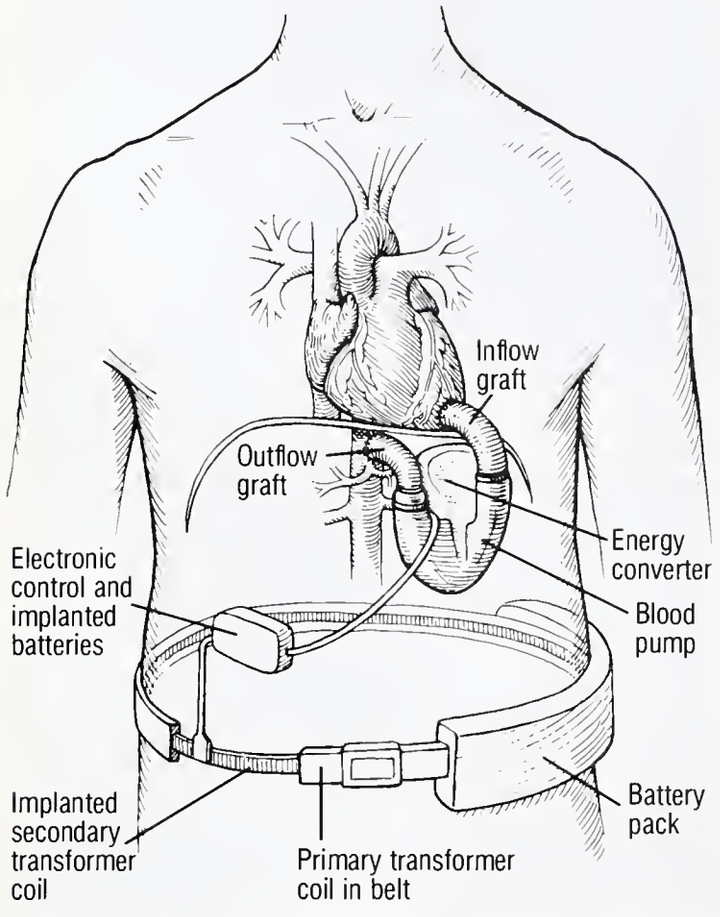

Figure 1.—The diagram shows a fully implantable, left ventricular-assist system (reproduced by permission of Devices and Technology Branch, National Heart, Lung and Blood Institute, National Institutes of Health).

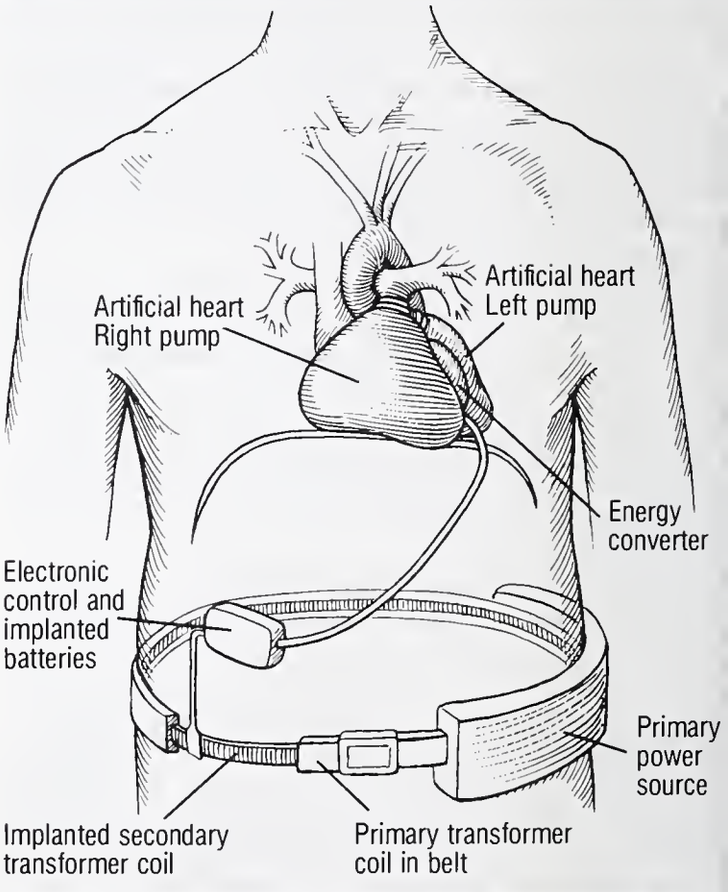

Figure 2.—The diagram shows a fully implantable, electrically actuated, completely artificial heart system (reproduced by permission of Devices and Technology Branch, National Heart, Lung and Blood Institute, National Institutes of Health).

ular function, were free of other coexisting disease and arrived at hospital at least two hours before death were considered to be potential candidates. Only about 14% of all patients who died of cardiac disease between ages 15 and 69 years (or 1.5% of all deaths in that age group) met those criteria. When these data were extrapolated to the US population to establish an order of magnitude, the potential number of candidates was in the range of 17,000 to 35,000. The major exclusion criteria were sudden death and coexisting disease. The average age of the potential recipients was 59 years, nearly 80% were male and the cause of ventricular failure in more than 50% was coronary artery disease.

The actual numbers will be influenced by the extent to which the device is accepted by society. The primary factor affecting societal acceptance is likely to be the performance record of the device—that is, does it work? In the case of other innovations, such as cardiac pacemakers or prosthetic valves and vessels, the fact that the devices were capable of carrying out their intended function in a very high percentage of cases contributed to both broadened public acceptance and expanded medical indications. Even without proof of efficacy, however, the specter of impending death is a powerful motivator for accepting heroic measures. For example, more than 200,000 coronary artery bypass graft procedures were done before effectiveness of the operation was scientifically evaluated, and even now a relatively small fraction of the 200,000 patients on whom the operation is carried out each year fit rigorously defined criteria. In our technologically oriented society, the public has come to accept, expect and even demand access to new medical procedures and devices. There is little reason to expect any difference in the case of the artificial heart; if the device is available, it will be used.

Issues related to cost—both to the individual patient and to society—will also play a role in determining the demand for the artificial heart. In 1963, at the time the artificial heart program was started, the cost of the device was estimated to be about $5,000. In the intervening years, five study groups have projected successively higher cost estimates.[7-11] The most recent study estimated that the cost of the device, its implantation and subsequent medical follow-up will be $150,000 (in 1983 dollars).[12] More than $100,000 of these costs are associated with hospital and medical care. Artificial Heart Program officials estimate that production costs for the device itself will initially be in the range of $40,000, but that this figure might be reduced to as low as $10,000 by economies of scale if the device were put into production. If one applies the $150,000 unit cost to the estimated range of possible recipients—17,000 to 35,000—then the cost to society might range between $2.5 and $5 billion per year. Some sense of the scale and proportion of these costs may be gained from comparison with society's costs for other procedures: cardiac pacemakers incur costs of $2 billion, the renal dialysis and renal transplant programs jointly cost more than $3 billion; the cost of a heart transplant is in the $60,000 to $120,000 range and liver transplants exceed $150,000. Thus, the projected cost for an artificial heart is likely to be in the same general range as many other expensive but accepted procedures and comparable to a number of medically acceptable procedures with unproved efficacy.

Pauker, a member of the Working Group on Mechanical Circulatory Support, has used modeling techniques to compare the costs and prognoses of patients treated with conventional medical therapy with those treated with an artificial heart.[12] In brief, using a model, a cohort of class IV cardiac patients were tracked through both courses of therapy over a defined period of time and the range of costs computed when a defined set of assumptions such as diagnostic procedures, hospital care, surgery and major and minor complications were entered into the model. In this study, class IV cardiac patients managed medically could be expected to survive for an average of less than six months and generate average medical costs of about $20,000, whereas identical patients treated with an artificial heart would be expected to survive 54 months at a cost of $150,000. That is, 48 months of additional survival might be "bought" at a cost of about $30,000 per year.

Quality of life must necessarily be a consideration in evaluating any medical procedure. It is a fact that the quality of life is compromised following many heroic procedures. Until actual experience has accumulated through controlled clinical trials, there is no way to predict with certainty what the quality of life will be for patients with an artificial heart. Even if the goal of an extended span of life is achieved and with a reasonable range of ambulation and activities, patients will not be able to forget they have the device. There will be individual adjustments to cues to the presence of the device such as noise, weight or vibration, to housekeeping requirements such as battery changes or anticoagulants or to the risks of more serious complications or the threat of device failure. The nature of the undertaking—permanent replacement of a vital organ—implies a trade-off between risk and benefit. Complications, both minor and catastrophic, are inevitable, and there will be a learning curve.

Ethical Issues

Medical economists have observed that dissemination of a new medical technology proceeds in the manner of a ratchet. That is, once accepted, the range of conditions or medical indications for a new device or technology tends to creep, and public acceptance, or even demand, makes the process irreversible. While the artificial heart is far from an accepted therapy, evidence has already accumulated that this phenomenon is likely to prevail.

Medical indications for cardiac replacement with either a mechanical device or organ transplant are sufficiently similar that the two approaches deal with overlapping patient populations. The development of a family of assist devices was based on a clinical strategy of providing short- to long-term assistance to a compromised ventricle, while the function of a total replacement device will be that of permanent and total cardiac replacement. Both assist devices and total replacement devices are already in use in several centers—and in a growing number of patients—as bridge devices, that is, to sustain candidates for cardiac transplant while awaiting the availability of a donor heart. It is inevitable that this application of mechanical cardiac devices will become more widespread and in the process will generate ethical dilemmas. Current medical criteria place the number of patients who might be accepted for cardiac transplant at a few thousand per year, but the number of donor hearts available for transplant has never reached 1,000 and is not likely to exceed 1,500 per year.[13] The use of an artificial heart device as a bridge cannot

increase the total number of transplants but will inevitably create ethical issues in patient selection.

The availability of an operationally successful, total artificial heart will have a substantial impact on our society: the number of possible candidates—17,000 to 35,000—speaks to the potential for societal benefit, but those numbers also introduce questions of how this scarce resource will be distributed and paid for. Health care in general is both a benefit and burden; the artificial heart is a special case in point. How much of society's resources should be allocated for health care? and, more specifically, how much of society's resources should be allocated to the artificial heart? Other questions involve how access is to be secured, which societal institution should deliver it and who should pay for it. Because the artificial heart has been developed from tax revenues, should not every citizen have the right to such, if needed? In fact, an earlier Congress declared that every citizen has the right to health care, but failed to provide either a definition or an appropriation. The questions of whether a person has a right to health and to health care and, if so, how much, were addressed in some detail by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research.[14] A realistic question is whether the right to health care differs from other basic needs such as food and housing. A practical answer is that medical care is not distributed any more equitably than other goods and services of society.

To these questions one must add that of whether one has a right to an artificial heart. It has been stated that our concept of rights is a political one that evolved from the works of Locke, Rousseau and others, who proposed rights as spheres of activity in which persons might be free from interference. That is, rights were defined as the claim of an individual against deprivation as, for example, the Bill of Rights, which holds that no one may be deprived of life, liberty or the pursuit of happiness. It is only recently that this concept has been transformed into a positive claim on society as, for example, the right to work or the right to health. The transformation has been clumsy and awkward. Expensive and scarce medical resources, such as the artificial heart, tend to complicate the issues, for the right to something necessarily implies the duty to provide it, which in turn raises the issues of who shoulders this obligation and to what extent it should prevail over the provider's own well-being. This is further complicated by the fact that rights tend to be asserted as absolute—that is, they "trump" concerns such as practicality and convenience. Further, there are in fact limits to all rights. A commonly cited example is that of free speech—freedom of speech does not confer the right to shout "fire" in a crowded theater. One analogy of this to health care may well be that people have a right to be protected against polluted water and air, infectious diseases and to other common public health measures, but some will hold that this right might well not extend to provision of an artificial heart.

Immediately following their discovery or development, new medical therapies and technologies often tend to be in short supply—for instance, penicillin or renal dialysis. This inevitably creates societal dilemmas over the means of equitably distributing these scarce resources. In general, society has evolved three mechanisms for allocating scarce resources. The marketplace is the actual basis on which most resources, including medical care, are distributed today. Regardless of whether the resource be primary and simple—immunization, glasses, teeth—or tertiary—computed tomographic scan, coronary artery bypass grafting, cesarean section—there is an economic gradient to access. The marketplace is clearly the primary mechanism by which scarce resources, including medical care, are allocated by the current administration. In contrast, the utilitarian distribution scheme would allocate scarce resources to persons on the basis of their worth to society. This was the criterion used 20 years ago by a committee appointed to select the limited number of patients who could be treated during the early development of long-term renal dialysis. This approach would be rejected today. Finally, the egalitarian approach is effectively a lottery in which all candidates have equal opportunity and is the approach favored by ethicists and philosophers. The 1973 Artificial Heart Review Panel recommended that under the circumstances in which artificial heart resources are scarce, the selection of candidates should be on the basis of medical criteria; that if the patient pool exceeds the supply, selection should be by random process, and, specifically, that ability to pay should not be a criterion. These general principles have subsequently been affirmed by other review groups.

The propriety of expending large amounts of money to develop an artificial heart has come under serious questioning. Can or should society use its resources for this purpose? Is the artificial heart the best way to invest the large sums that will be required, and are there better alternatives? Could these resources better be invested in programs of immunization, prevention, nutrition, smoking education and so forth? These are not simple issues. Not all are willing to accept the argument that our resources are limited, nor that the nation's medical expenditures should be pegged at an arbitrary level, such as 10% of the gross national product. Others will hold that resources are finite and hence expenditures for an artificial heart will necessarily displace expenditures for public health measures, or medical research or even expenditures for the goods and services of society, such as food, welfare, national defense, alcohol abuse prevention and the like.

Summary

These complex issues cannot be resolved in the hour allocated for this conference. Some summary comment may be made, however. A starting point might be the question of whether development of the artificial heart should proceed. The facts are that it would be impossible to suppress further development—it is inevitable that fully implantable artificial hearts will continue to be developed. The intellectual resources are mobilized and committed, technology is at hand and the need and patient population have been identified. The technology is not proprietary within the United States; parallel programs have been under way in several countries and have reached advanced stages of development, notably in Japan and Germany. There is capital both here and abroad to manufacture the device. It remains only to specify whether one wishes a Buick or a Toyota.

A second question might be whether there will be patient demand. The data seem clear that a population will exist that could benefit. It seems extremely likely on the basis of recent experience with pacemakers, transplantation, coronary artery

bypass grafting, heart transplant and other procedures that the public and their physicians and surgeons will want and expect this device. The number is likely to be large enough to provide a market, and, in the manner of other new technologies, the medical indications for these devices are likely to expand. Experience also dictates that hospitals will compete for franchises.

There remains the question of resource allocation. The likelihood seems great that society will deal with this issue as it always has. Our current system of medical practice dictates that those people who want the device and can pay for it will probably get it, in much the same way they currently buy other medical goods and services. Our society, however, also has a strong ethic of rescue. It seems inevitable that availability of the device will become more nearly universal, and, whether by fees, premiums, taxes or special set-aside for entitlement, the costs will be paid by people.

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Advances in the Management of Cardiac Arrest

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD:* *The topic of this discussion is advances in the management of cardiac arrest. Dr Callaham is an adjunct associate professor of medicine and director of our Division of Emergency Medicine here at the University of California at San Francisco. He is a graduate of this medical school and trained in emergency medicine at the University of Southern California. He is a member of the Council of Academic Societies of the American Association of Medical Colleges and is the associate editor of* Annals of Emergency Medicine. *In addition, Dr Callaham has a particular interest in toxicology and cardiac pharmacology.*

MICHAEL CALLAHAM, MD:† Thank you, Dr Root. The topic of cardiac arrest is so broad, and its literature so voluminous, that it is not possible in this limited space to cover the major portion of it. There are many studies on such intriguing subjects as improving the mechanical efficiency of cardiopulmonary resuscitation—such as by interposed abdominal compressions, varying the rate or duration of chest compression or simultaneous compression-ventilation—and new drugs such as glucagon. There is not enough evidence, however, to warrant the clinical use of these particular measures at present. In this discussion I will therefore focus on a few specific topics, particularly pharmacology, where clinically significant advances have recently been made. "Advances" may be a misleading term. Most of the progress has actually been made by reexamining important questions that had been previously poorly studied or overlooked and eliminating many of the unsupported practices and recommendations of previous advanced cardiac life-support (ACLS) guidelines.

Although this discussion focuses on our new understanding of the pharmacologic management of cardiac arrest, clinicians should not forget that far and away the most effective treatment of ventricular fibrillation is rapid defibrillation within the first minutes of arrest, followed by ventilation. The success of any therapy after that time is dramatically reduced, and most of the drugs recommended in ACLS guidelines have been poorly studied or never studied in patients with cardiac arrest. Electromechanical dissociation and asystole have no proven therapy and the probability of survival to discharge from hospital is still only about 2% to 3%.

Clinicians should also note the limitations of the cardiac arrest literature, almost all of which consists of studies conducted in healthy dogs with normal coronary arteries and under the influence of anesthetics that dramatically alter cardiac function. Studies in humans are rare, and even rarer are studies examining more than the first hour or two after arrest. Study protocols vary widely and many experimental models involve unrealistically brief periods of arrest. It is difficult to know how to apply these results to typical elderly human patients with stenotic coronary vessels who in many cases are taking several medications with cardiovascular effects.

A final word of caution regarding the ACLS guidelines themselves: The goal of training most physicians, nurses and paramedics to be sophisticated providers of cardiac care may be laudable. The guidelines, however, are confusing in their frequent lack of distinction between true cardiac arrest and the various cardiac dysfunctions that occur in a variety of disease states that are pathophysiologically very different from arrest. Furthermore, many past ACLS recommendations have been founded on only portions of the relevant published studies or very poorly reflected the clinical implications of those studies. Additionally, by their very nature, the ACLS guidelines are always at least several years out of date. The existence of ACLS certification has led many clinicians to conclude that these guidelines are the standard of care. The authors of the ACLS guidelines state, however, that the guidelines "were not intended to imply that justifiable deviations from suggested standards and guidelines by physicians qualified and experienced in cardiopulmonary resuscitation . . . represent a breach of a medical standard of care," nor that "new knowledge, new techniques, clinical or research data, clinical experience or clinical circumstances may not provide sound reasons for alternative approaches to cardiopulmonary resuscitation."[1] Thus, the ACLS guidelines are merely a starting point and a frame of reference for clinicians who frequently deal with cardiac arrest, and truly optimal care for such patients requires intelligent deviation based on

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ABBREVIATIONS USED IN TEXT

ACLS = advanced cardiac life support
P_{CO_2} = partial pressure of carbon dioxide

experience, the results of new studies and critical reading of the literature.

Adrenergic Drugs

Epinephrine has been used for resuscitation from cardiac arrest since 1906.[2] Most clinicians, however, have little understanding of the pharmacologic characteristics of adrenergic drugs in cardiac arrest, which are quite different from those in a perfusing heart. Knowledge of these characteristics is particularly important now because studies and recommendations that were uncritically accepted and put into practice some 25 years ago are now being questioned.

Between 1965 and 1968, Joseph Redding completed the studies that are still the foundation of the ACLS guidelines. He determined in dogs that epinephrine, phenylephrine and methoxamine (the latter two being pure α-adrenergic agents) were all effective in restoring spontaneous circulation about 90% of the time, whereas without these drugs resuscitation rates were 20% or less. The benefit occurred only when the drugs were given early and did not involve aiding in defibrillation. Noteworthy among these early results are that methoxamine was usually the most effective drug in resuscitation and the use of isoproterenol produced no survivors, a result consistently worse than no drug treatment at all.[3] Results of subsequent studies in animals have confirmed the effectiveness of epinephrine in reestablishing spontaneous circulation after cardiac arrest.[3-5]

The next logical question is by what mechanism epinephrine and other catecholamines accomplish these benefits. Epinephrine increases heart rate, contractile force, arterial blood pressure, systemic vascular resistance and automaticity in a perfusing heart, but its activity during cardiac arrest is very different. Epinephrine does not aid in defibrillation but does increase the likelihood of restoration of circulation after conversion to a perfusing rhythm.[2-6] The benefit of epinephrine in cardiac arrest was traditionally thought to stem from its α-adrenergic effect of peripheral vasoconstriction, which raises peripheral vascular resistance and increases the aortic diastolic pressure.[2] Because the aortic diastolic pressure minus the right atrial diastolic pressure equals coronary perfusion pressure, the aortic diastolic pressure is a major determinant of coronary blood flow. Subsequent studies showed a consistent and linear relationship between coronary perfusion pressure, aortic diastolic pressure and resuscitation success.[7-11] If an aortic diastolic of about 40 torr, or a coronary perfusion pressure of about 20 torr, cannot be achieved, the heart cannot resume effective contractions. This elevation of coronary perfusion pressure is due solely to α-adrenergic vasoconstrictor effects. α-Blockade before experimental arrest produced as few resuscitations with epinephrine as no treatment at all, whereas β-blockade had no effect.[4,12] Pure α-adrenergic agents such as phenylephrine or methoxamine are experimentally as effective or more effective than epinephrine.[5,13,14]

β-Adrenergic activity is not helpful in resuscitation from arrest, but could it be harmful? Two β-adrenergic effects are of concern—vasodilatation and inotropic effects in fibrillation. Because β-adrenergic drugs cause vasodilatation, it could be predicted they would cause a drop in diastolic and perfusion pressure and worsened results. In fact, this was first shown in 1965; administering isoproterenol lowered the diastolic pressure from 18 torr with no treatment to 12 torr. Only 9% of animals could be resuscitated and none survived to two hours (as compared with 30% and 20%, respectively, with no drug treatment at all).[3] Although these data were as convincing as those that led to the use of epinephrine, they were ignored and ACLS guidelines had recommended the use of isoproterenol in cardiac arrest until the 1986 revision, when it was finally dropped. Isoproterenol lowers vascular resistance during cardiopulmonary resuscitation and shunts blood through muscle and nonvital organs, to the detriment of the heart and the brain (Figure 1).[15] Coronary perfusion pressure and measured coronary blood flow in patients in cardiac arrest with the use of isoproterenol was only 60% as great as that with saline and only 19% of that with epinephrine.[11,15] Administering dobutamine, another predominantly β-adrenergic drug, produced resuscitation rates close to those of no treatment, in pronounced contrast to α-adrenergic agents.[16] The literature unequivocally shows that β-adrenergic drugs such as isoproterenol are harmful and are contraindicated in cardiopulmonary resuscitation; the 1986 ACLS guidelines have recognized this and ceased recommending the use of isoproterenol in patients with arrest.[1]

The same logic suggests that the use of isoproterenol in a patient with bradycardic hypotension might also be harmful if the blood pressure were being maintained primarily by vasoconstriction. In a study of prehospital patients receiving the drug for this indication, 48% had improvement, but 28% had no change in pressure, 12% had a drop in pressure and 12% suffered cardiac arrest and died.[17] Clearly, β-adrenergic drugs like isoproterenol possess major risks even when used after resuscitation from arrest.

Epinephrine possesses another potentially harmful β-adrenergic effect: it increases the vigor of fibrillation.[18] This does not, as often claimed, increase the likelihood of defibrillation,[19] but it does further increase coronary vascular resistance and decrease coronary blood flow. Because the oxygen needs of a fibrillating heart are virtually the same as those of a beating one,[20] all these effects would be predicted to worsen

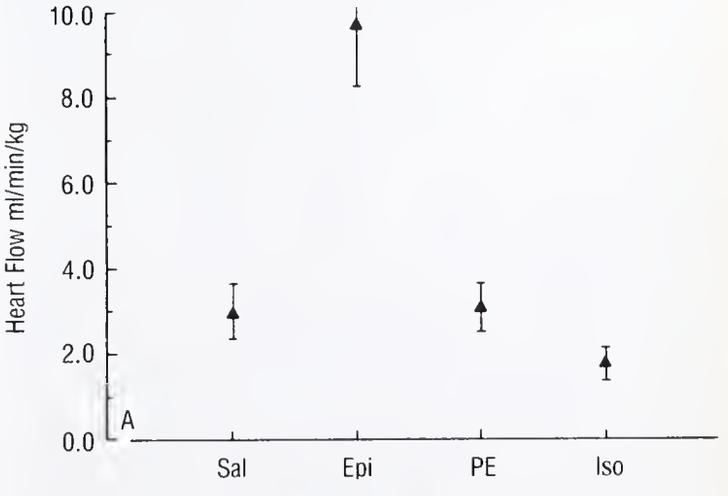

Figure 1.—Myocardial blood flow during cardiopulmonary resuscitation is diminished by isoproterenol (Iso) as compared with epinephrine (Epi), phenylephrine (PE) and saline (Sal) (from Holmes et al[15]).

myocardial ischemia and hypoxia. Epinephrine also reverses the normal preferential blood flow to the subendocardium, worsening its ischemia—an effect not produced by methoxamine.[18]

If the benefits of catechols in arrest are due solely to α-adrenergic effects and β-adrenergic effects are harmful, which catechol should we be using? The same studies that proved the efficacy of epinephrine suggested that methoxamine, a pure α-adrenergic agent, was superior.[5] Unfortunately, although the superiority of methoxamine has been well shown for the immediate return of circulation, it has never been studied in terms of effects beyond a few hours in a model of the current treatment of arrest. Methoxamine hydrochloride, unlike epinephrine, has a duration of action of several hours and its use could substantially affect postresuscitation cardiovascular dynamics, so studies of longer duration would be essential before its clinical use could be contemplated. Administering phenylephrine hydrochloride, a pure α-adrenergic agent with a duration of action longer than epinephrine but shorter than methoxamine, has been as effective as the use of epinephrine in resuscitation.[3,5] There is conflict, however, between experimental studies that show it provides inferior brain perfusion[21] and studies in animals that show 24-hour survival and a neurologic state equivalent to that with the use of epinephrine.[22] Norepinephrine bitartrate, with its strongly α-adrenergic activity and short duration of action, seems a very logical choice but has never been studied.

Although not recommended in the ACLS guidelines, dopamine hydrochloride is often used in cardiac arrest. Only one study has ever been done of its use in cardiac arrest.[16] Although it was effective, the dose in this study was an intravenous bolus of 2 mg per kg of body weight, which is an extremely α-adrenergic dose virtually never used in clinical practice. Dopamine offers no proven or theoretic advantage over epinephrine and in typical doses would be expected to be as harmful as isoproterenol hydrochloride. Thus, epinephrine remains far and away the best studied and most effective catecholamine and the only one whose use can presently be justified.

The optimal dose of epinephrine is another unknown. Redding in his pioneering work used 1-mg doses in 20-kg (44-lb) dogs, yet a dose of 0.5 to 1 mg is suggested for adults in the ACLS guidelines, which does not vary with body weight. Until recently, no studies of the optimal dose of epinephrine in cardiac arrest existed, although Redding and Pearson did show that 0.2 mg in dogs (about the same dose by weight suggested in the ACLS guidelines) was not effective.[23] Recent studies have found that doses of 100 to 200 μg per kg (instead of the typical ACLS-recommended doses of 7.5 to 15 μg per kg) produce greater and more prolonged elevation of diastolic pressure (Figure 2).[24] Ironically, these are about the same microgram-per-kilogram doses first used in the pioneering studies of Crile and Dolley in 1906.[2] In a study examining the threshold dose for successful resuscitation in dogs, four out of five successful intravenous doses were double the ACLS-recommended human values, and the mean was 14 μg per kg (Figure 3).[25] The same study found the ACLS-recommended endotracheal dose of epinephrine too low by a factor of ten; the mean dose needed for successful resuscitation by this route was 130 μg per kg. Even more recent investigation found that doses of 200 μg per kg produced cerebral and myocardial blood flows approaching normal; 20 μg per kg produced flows compatible with neuronal survival only in the medulla and spinal cord. Doses of 2,000 μg per kg produced no additional cerebral benefit.[26] Myocardial blood flows at doses of 200 μg per kg were 100 times greater than at 20 μg per kg, but declined somewhat at 2,000 μg per kg.[27] No ill effects of the use of higher doses (such as postresuscitation hypertension, ischemia or dysrhythmias) have been noted, probably due to the short half-life of epinephrine, but seeking such effects was not the purpose of any of these studies.

The current maximum ACLS-recommended epinephrine dose of a 1-mg bolus given intravenously every five minutes is equivalent to 3 μg per kg per minute in a 70-kg (154-lb) adult. This is probably a homeopathic dose. Based on the literature, a more reasonable course of action, if resuscitation is not successful within a few minutes, is to administer 100 to 200 μg per kg as an intravenous bolus every five minutes, or to place the contents of a 30-mg vial of epinephrine in 250 ml of fluid and give this as an infusion at 20 to 40 μg per kg per minute. Although these dosages are fairly arbitrary, they are no more so than the current recommendation. Because every minute reduces the likelihood of resuscitation and because epinephrine is the only drug conclusively proved effective in

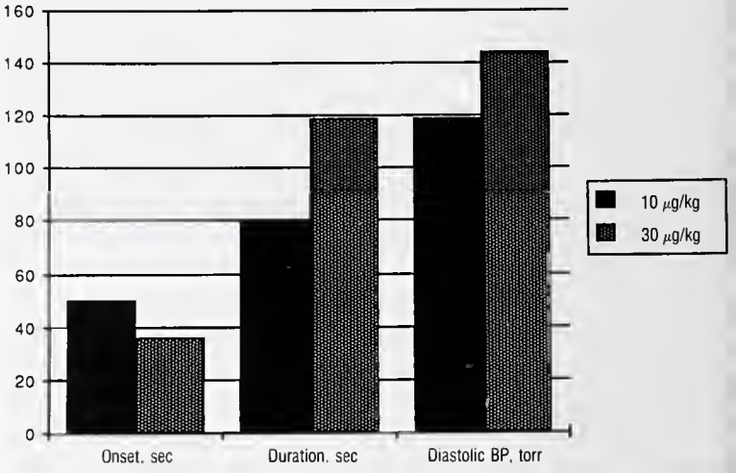

Figure 2.—The graph shows the pressor effects of varying bolus doses of epinephrine in cardiac arrest. The typical doses recommended by advanced cardiac life-support guidelines are 7.5 to 15 μg per kg bolus (from Kosnik et al[24]). BP = blood pressure

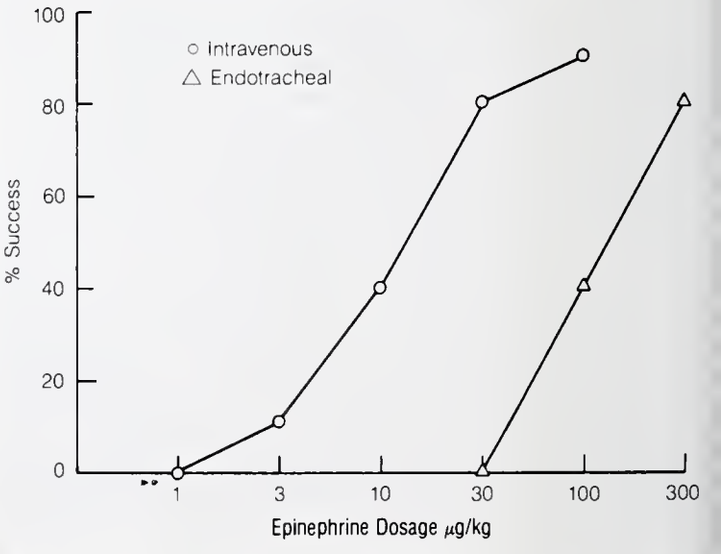

Figure 3.—The graph shows the relationship of increasing doses of epinephrine to the success of resuscitation in animals, by both endotracheal and intravenous routes (from Ralston et al[25]).

resuscitation, the benefit of larger doses is worth the theoretic risk.

Acidosis and Bicarbonate

Since the inception of the ACLS guidelines, aggressive treatment of acidosis with sodium bicarbonate has been recommended. This practice is based on very little scientific evidence, however. Only two studies appear to support the initial ACLS recommendation of bicarbonate use.[5,6] These small studies with short arrest times showed that, as expected, bicarbonate increased the pH of treated animals to levels of 7.6 to 7.9 and increased their arterial partial carbon dioxide pressure (P_{CO_2}) about 10 torr. Bicarbonate alone did not facilitate resuscitation[5] and when given with epinephrine its benefit was that of improving circulatory status after arrest. This is not surprising, since the beneficial effects of bicarbonate in patients with acidosis due to shock are entirely explained by its hyperosmolarity and sodium load, not its effect on pH, and can be duplicated by using hypertonic saline or mannitol.[28] No study of the use of bicarbonate in patients with cardiac arrest has ever controlled for these variables.

In patients not having acidosis before arrest, arterial metabolic acidosis develops slowly over the first 20 to 30 minutes and seldom goes below a pH of 7.2.[11,29,30] This is of particular significance because virtually all successful resuscitations are accomplished within this same time frame.[31,32] In fact, metabolic acidosis is not severe in cases of arrest; the primary acid-base disorder is a very severe respiratory acidosis (with a mixed venous P_{CO_2} averaging 70 to 90 torr) that develops due to the inability to excrete carbon dioxide via the impaired pulmonary circulation.[33,34] This severe respiratory acidosis represents the true acid-base status of the tissues and can only be measured in venous blood gases, not the arterial blood gas measurements routinely done. Such respiratory acidosis severely and rapidly depresses cardiac function. Anything that further elevates the P_{CO_2}, such as hypoventilation or administration of bicarbonate, would of course worsen this respiratory acidosis.

Metabolic acidosis, by contrast, may not be a particularly harmful state in patients with cardiac arrest. Metabolic acidosis does not in any way affect the amount of energy needed to defibrillate the heart,[35] nor does it increase the incidence of electromechanical dissociation.[36] Although acidosis blunts the response of the cardiovascular system to catechols in a perfusing heart, this blunting is usually moderate (about 30% in animals), it can be reversed with hyperventilation and there are no data to suggest it cannot be overcome with larger doses of catechols.[37–39] (The effect of acidosis on catechols in cardiac arrest has never been studied). Although cardiac function is depressed by acidosis, the determining factor is intracellular pH, not extracellular as measured by arterial blood gases. The intracellular pH declines only very gradually with metabolic acidosis in a nonlinear fashion[40–42]; cardiac tissue is particularly well buffered intracellularly against metabolic acidosis.[43] Accordingly, both cardiac conduction and contractility are only moderately and gradually decreased in the first 20 minutes with metabolic acidosis (Figure 4).[41,42,44] Hypoxia, not acidosis, accounts for most of the cardiac depression.[45] Respiratory acidosis, however, produces immediate and profound depression because carbon dioxide immediately enters cells and induces intracellular acidosis.[41,42,44]

Metabolic acidosis, in fact, has the beneficial effect of decreasing the affinity of hemoglobin for oxygen and thereby increasing the partial oxygen pressure. This is not just a theoretic effect; the actual measured oxygen extraction during shock increases with acidosis, particularly in vital organs.[46] In addition, metabolic acidosis protects the myocardium against hypoxia. Isolated hypoxic heart muscle kept at pH 6.8 by metabolic means regains 100% of normal contractility after 15 minutes of oxygenation but when kept at pH 7.4 never regains more than 50% contractility, presumably due to preservation of cellular adenosine triphosphate (Figure 5).[45] Similar results have been found when studying hearts stored for 24 hours in cardioplegic solutions for transplant.[47]

Despite the clinical importance of this problem, only one experimental study has focused on the relationship of acidosis to survival in arrest.[23] Conducted by one of the pioneers of resuscitation research at the same time as other studies that laid the foundation of ACLS guidelines, it found that no matter what the drug treatment, animals successfully resuscitated invariably had *more* acidosis—often with a pH of less

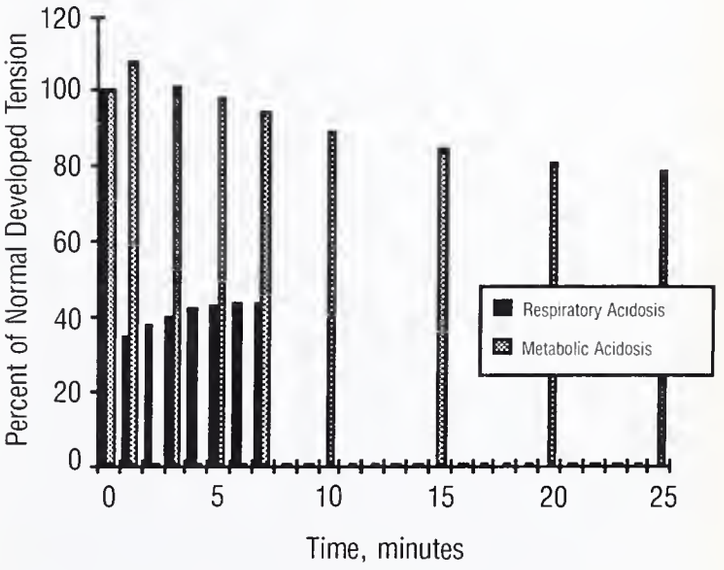

Figure 4.—The graph shows the effect of a pH of 6.8 attained by respiratory or metabolic acidosis on the developed tension of a perfused adult rabbit heart. Respiratory acidosis causes an immediate and profound drop in developed tension; the change with metabolic acidosis is slower and less severe (modified from Nakanishi et al[42]). The effect on conduction velocity is virtually identical (from Kagiyama et al[41]).

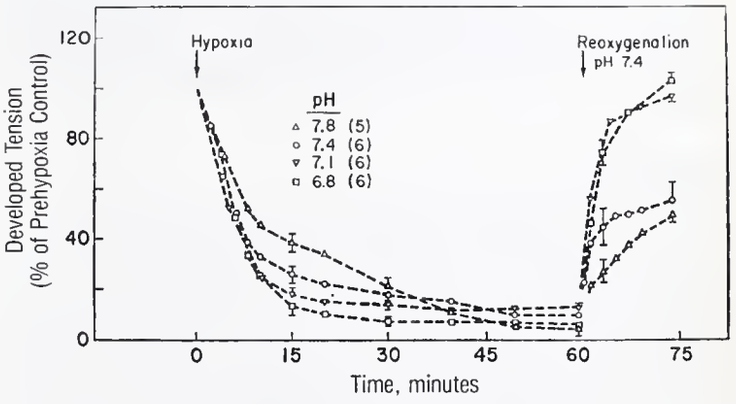

Figure 5.—Hypoxic cardiac tissue regains normal contractility after reoxygenation when kept at an acidotic pH, but not when kept at a normal or alkalinic pH. Note that most loss of contractility is caused by hypoxia, not pH variations (from Bing et al[45]).

than 7.1—than those not resuscitated (Figure 6). These results seem to have been ignored, however, and recommendations for bicarbonate use continued. A recent study in humans documented that a pH of 7.55 or greater was associated with decreased survival, and that comparable degrees of acidosis had a much smaller impact on outcome (Figure 7).[29] There is thus no convincing evidence that the degrees of metabolic acidosis seen in patients with cardiac arrest are of major concern. Even in the perfusing state, metabolic acidosis may be more a symptom than a cause of a pathologic process.[48]

By way of contrast, the use of bicarbonate has long been known to present the risks of alkalosis, hypernatremia and hyperosmolarity, all of which are easily and commonly accomplished with typical ACLS-recommended doses and are predictors of an unsuccessful outcome.[29] Although bicarbonate may reassure unwary clinicians by returning an arterial pH to normal, it also inevitably elevates the P_{CO_2} because it must generate this gas to buffer hydrogen ions. Bicarbonate is a useful buffer only when carbon dioxide rapidly dissipates, the very opposite of the situation in cardiac arrest. A partial pressure of carbon dioxide will rise even in a well-ventilated patient with cardiac arrest, and in a poorly ventilated patient or in ischemic areas of circulation, elevation of the P_{CO_2} will be severe. Carbon dioxide generated by bicarbonate instantly enters the cell (which metabolic acids cannot) and greatly depresses cardiac conduction, the cardiac index and contractility after resuscitation (Figure 4).[36,41,49] In shock states, administering bicarbonate greatly worsens blood pressure, cardiac index and lactate production.[50] Bicarbonate makes cerebrospinal fluid acidotic—which it normally is not in arrest[30]—and decreases cerebral blood flow to half of normal in infants with hypoxia.[51] These decreases are probably due to hypoxic damage to the blood-brain barrier, which permits bicarbonate to induce cerebral vasoconstriction at a time when brain perfusion is already inadequate. Bicarbonate may in fact increase the postresuscitation brain injury caused by central nervous system acidosis and hypoperfusion.

There does not seem to have ever been sound scientific evidence for a beneficial role of the use of bicarbonate in cardiac arrest. Each subsequent version of the ACLS manual has lowered the recommended dose, and the latest guidelines now state that it be given only at the "discretion of the team leader."[1] Because no benefit has ever been proved at any pH, and because the harmful effects, both theoretic and documented, are common and real, its use in cases of arrest should be abolished. It seems likely that its use as a treatment of any form of metabolic acidosis will come under increasingly critical scientific scrutiny, which is likely to result in its abandonment.

Conclusion

The most successful treatment for ventricular fibrillation remains defibrillation. For patients with cardiac arrest in general, a rapid early response and effective ventilation are vital, and successful results must be obtained within the first 20 minutes if they are to occur at all. The role of epinephrine in increasing coronary perfusion pressure and the likelihood of the return of circulation is well established, and currently recommended doses are probably at the very low end of the therapeutic spectrum. Administering bicarbonate has never been shown to be of any benefit, it has many harmful effects

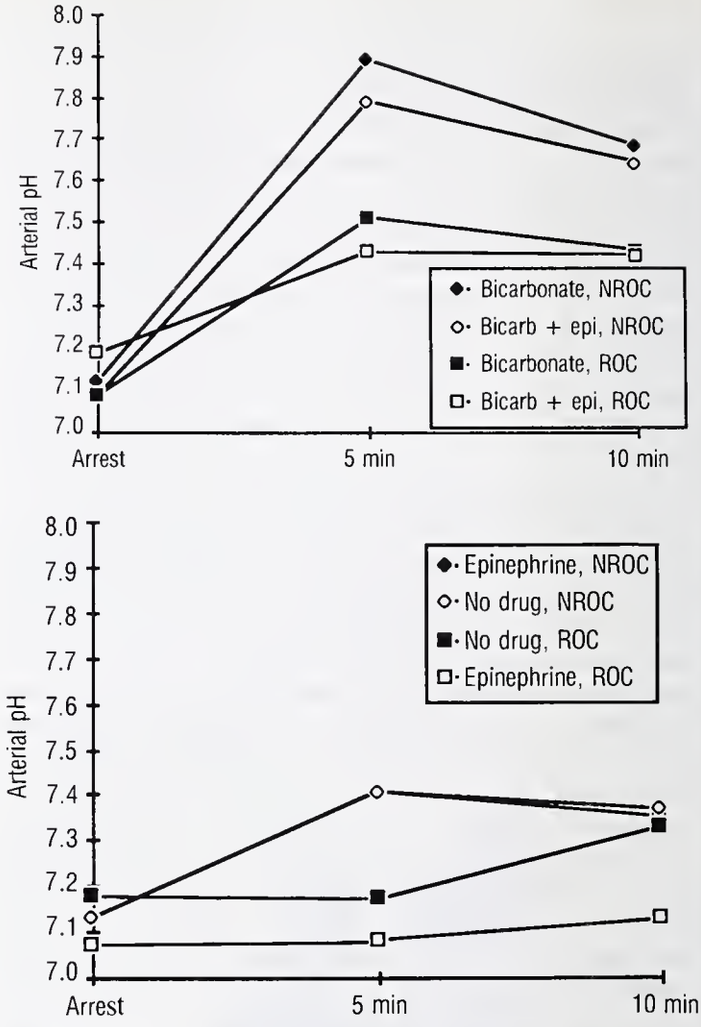

Figure 6.—(Both graphs) Regardless of treatment, animals with return of circulation (ROC) had more acidosis at all stages of arrest than those with no return of circulation (NROC). As expected, bicarbonate administration produced profound alkalosis (from Redding and Pearson[23]). epi = epinephrine

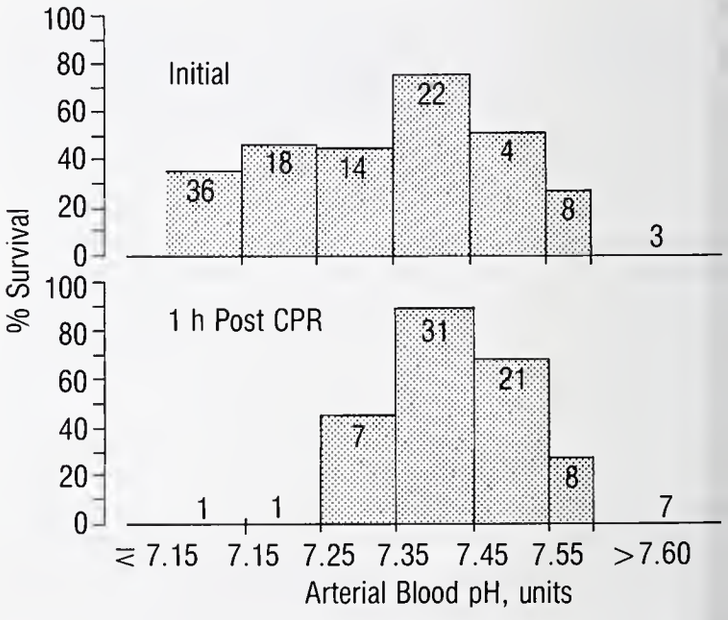

Figure 7.—Both initially (within 10 minutes of arrest) and one hour later, a pH of 7.55 or greater was associated with a lower survival rate. Comparable degrees of acidosis produced higher survival rates than alkalosis (for instance, there was 45% survival at a pH 0.1 to 0.2 below normal, but only 25% survival at a pH of more than 0.1 above normal) (from Well et al[29]). CPR = cardiopulmonary resuscitation

that are likely to worsen the chances of resuscitation and its use should be abandoned. Clinicians who seldom resuscitate patients from cardiac arrest should regard the ACLS guidelines as a useful practice of mechanical skills; clinicians who manage arrest frequently should regard the guidelines only as a starting point for a critical and constant reading, interpretation and implementation of the scientific literature.

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Epitomes
Important Advances in Clinical Medicine

General and Family Practice

The Scientific Board of the California Medical Association presents the following inventory of items of progress in general and family practice. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in general and family practice that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General and Family Practice of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Genital Herpes Infections

THE NUMBER of genital herpes infections has increased dramatically over the past decade. With an estimated 300,000 new cases and 9 million recurrences per year, herpes may, in fact, be the most prevalent of all sexually transmitted diseases.

Herpes simplex virus (HSV) type II is the agent chiefly responsible for genital infections, although type I is present in a small percentage of cases. The infection is usually transmitted by sexual contact with someone who has active disease. In some situations, the infection may be a reactivation of the virus from a quiescent phase following a previous infection. Apparent but not well-understood triggers of the reactivation process include emotional distress, menstruation and pneumococcal and meningococcal infections.

Herpes genitalis can usually be diagnosed by history and physical examination alone. Several days after sexual contact with an infected partner, a person may have local symptoms of discomfort and systemic symptoms of fever, headache, myalgias and groin adenopathy. The herpetic lesion that appears progresses from a papule initially to a vesicle and then an ulcer that usually heals without scarring. Unfortunately, although most recover uneventfully from the primary episode, more than two thirds of those infected typically have more than five recurrences per year.

Viral culture remains the method of choice for confirming the presence of genital herpes infections. Antigen testing using fluorescein-immunoperoxidase assay methods alone have improved but are not yet readily available. The Tzanck cell test and Papanicolaou test can be done in office but have low sensitivity and specificity. Serologic testing has not proved to be practically useful.

The management of genital herpes is palliative rather than curative. Topical acyclovir may be used to reduce symptoms of a first episode. Acyclovir may be given orally to treat initial episodes (200 mg five times a day for ten days) or individual recurrences (200 mg five times a day for five days). If a person has at least six to eight recurrences per year, suppression therapy may be indicated (200 mg three times a day for as long as six months). Continuous treatment beyond six months has not yet proved safe or effective.

For those pregnant women who have a history of herpes genitalis or known exposure, cervical cultures are done weekly late in the third trimester. If HSV is detected within two weeks of delivery and membranes have been ruptured less than four hours, a cesarean section is recommended. About 40% to 80% of infants born through an infected birth canal are affected and face a mortality rate of 60%.

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Exercise Prescription

EXERCISE PRESCRIPTION is in the process of rapid growth and redefinition. Until recently, the term "exercise prescription" has been thought by many to be synonymous with "aerobic exercise prescription," largely through the pioneering work of Kenneth Cooper and others. The basic requirement for maintaining aerobic fitness is to achieve 70% of the predicted maximal heart rate for 10 to 15 minutes three times a week. This concept has been widely accepted. Exercise physiologists and physical therapists have called for an expansion of this concept to exercise prescription. They have recom-

mended that strength, flexibility and coordination training should be a part of any exercise prescription.

Strength training is exercise that increases muscular strength. Low-weight, high-repetition strength exercises for general fitness are now recommended. Low-weight, high-repetition exercises are exercises that can be done for 10 to 15 repetitions using free weights or machines before the onset of muscular fatigue. The advantage of low-weight, high-repetition exercise is that it is nearly as effective as high-weight, low-repetition exercise (exercise where muscular fatigue sets in with only a few repetitions) in strength gain, but it does not predispose to significantly high elevations in blood pressure, as does high-weight, low-repetition exercise.

Flexibility training, or muscle stretching before and after exercise, has been much discussed but little studied. A systematic stretching program ten minutes before and after exercise, however, is recommended as part of every exercise prescription.

Coordination training is conceptually the most complex part of exercise prescription. Globally, it is the practice of sports-specific techniques that enhance neuromuscular coordination with the goal to prevent injury. Charles Henning, MD, Clinical Associate Professor of Orthopedics at the School of Medicine, University of Kansas Medical Center, has data showing that a series of practice techniques has decreased the incidence of anterior cruciate ligament injuries in school athletics in his community. Teaching athletes how to fall safely, decelerate, pivot and change direction while running are examples of Henning's techniques.

The "fitness boom" is a popular trend in American culture. Many family physicians are being called upon by patients to "prescribe exercise." Exercise prescription should include aerobic, strength, flexibility and coordination training techniques. Consequently, family physicians need to know that exercise prescription, when properly given, will lead to the long-term goals of promoting health and preventing injuries.

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Ultrasound in Obstetrics—Safety Considerations

Ultrasound has become so commonplace in obstetrical practice that it is almost routine. The 1984 consensus statement of the National Institutes of Health listed 27 indications for diagnostic ultrasound imaging in pregnancy. With the use of Doppler ultrasound to detect fetal heart tones, imaging ultrasound and ultrasonic devices for external fetal monitoring, most pregnant women will have multiple exposures to ultrasound. Many pregnant women wonder whether ultrasound is completely safe in pregnancy, and some refuse its use based on a fear of risk to the infant.

The bioeffects of ultrasound have been extensively studied. Ultrasound energy can cause tissue damage by two known mechanisms—heat and cavitation. The intensity of ultrasound required to cause these effects in humans is not achieved in commercially available devices used in pregnancy. Also, most of the ultrasound-produced heat is absorbed by a mother's tissues and does not reach the fetus. Hence, after analyzing experiments on ultrasound effects, the National Counsel on Radiation Protection has reported that currently available imaging and Doppler ultrasound devices are safe in pregnancy.

Some authors still express caution about the indiscriminate use of ultrasound in pregnancy. They state that all possible biologic effects may not be known and that a large enough epidemiologic study to detect injury in 1 in 5,000 infants (the estimated chance of leukemia in a fetus exposed to x-rays) has not been done. Such uncertainty prompts the International Childbirth Education Association to request that informed consent be given by pregnant women before exposure to ultrasound. While a formal procedure for consent may not be necessary, physicians should discuss the use of ultrasound with their patients and limit its usage to situations in which the information obtained is important in managing the pregnancy.

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Maternal Serum α-Fetoprotein Screening

A recent California law, administered by the Department of Health Services, mandates all prenatal care providers to offer maternal serum α-fetoprotein (MS-AFP) testing, with appropriate informed consent, to all patients during the 15th to 20th week of gestation. This law reflects the acceptance of many authorities of the MS-AFP test as a well-established screen for certain birth defects and it parallels an official recommendation by the American College of Obstetricians and Gynecologists. It therefore seems prudent that all family physicians practicing obstetrics understand the basic premises, limits and implications of MS-AFP screening.

Neural tube defects occur in about one in every thousand live births and are the cause of fetal and infant death and serious handicaps in survivors. Prenatal diagnosis by amniocentesis and elective abortion for expectant mothers with a known family history of neural tube defects have been available for years and are based on leakage of AFP through the open fetal defect. Of infants with such defects, however, 90% to 95% are the first affected child in a family; therefore, the discovery that AFP could be measured in maternal serum led to a simpler screen.

A large number of prospective studies have shown high sensitivity (95%) for anencephaly and slightly lower sensitivity (70% to 75%) for open spina bifida. In addition, a recent discovery that lowered levels of MS-AFP are correlated with the Down syndrome (20% to 40% sensitivity) now allows screening for women younger than 35 years.

Despite its high sensitivity for neural tube defects, the MS-AFP test has a very poor specificity because it is esti-

mated that 8% of women tested will have a positive result, but 6% of these will actually have a fetal abnormality or pregnancy complication diagnosed—that is, 94% false-positives. Follow-up evaluation of a positive test includes repeat testing, ultrasonography and, finally, amniocentesis and is best handled by referral to perinatal specialists. Problems associated with a positive result, other than neural tube defects, include twin gestation, miscalculated gestational age, ventral wall defects (omphalocele and gastroschisis), increased risk of fetal loss and low birth weight. It is hoped that early recognition of these may also prove beneficial.

Family physicians should accurately inform their patients of the above information, make appropriate referrals if a positive result occurs and, most important, be ready and available to offer emotional support to a patient in deciding whether to undergo screening, dealing with a positive screening result and dealing with the follow-up process and its ultimate result.

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Passive Smoking

ALTHOUGH THE HEALTH RISKS of smoking have been known for decades, the dangers of passive (involuntary) smoking have come to light relatively recently. The measurement of plasma, urine and saliva cotinine concentrations has provided us with an accurate and reproducible method of assaying the quantity of tobacco smoke passively inhaled. Through this method, it has been estimated that in a home in which only the father smokes, a child inhales the equivalent of 30 "actively" smoked cigarettes per year. If only the mother smokes, the child inspires the equivalent of 50 actively smoked cigarettes per year and, if both parents smoke, the child smokes 80 cigarettes a year.

Therefore, it is not surprising that the health risks of passive smoking are substantial, particularly in the very young. A number of studies have found decrements in pulmonary function among children of smoking parents as compared with children of nonsmoking parents. Similar studies have found increased rates of bronchitis, pneumonia, persistent middle ear effusion and sudden infant death in children of parents who smoke. There is also some concern that parental smoking may diminish childhood growth but, to date, the data are conflicting.

Adults are not spared the health hazards of passive smoking. Studies have related passive smoking to small airways dysfunction, decreased exercise performance, lung cancer and ischemic heart disease. Passive smoking appears to lower the exercise threshold necessary to produce chest pain in patients with angina pectoris and may trigger asthmatic attacks in some patients who suffer from asthma.

Unlike active smoking, passive smoking largely harms people who choose *not* to smoke; therefore, smokers who cannot relinquish the habit must be educated about the risks of passive smoking and instructed to smoke outdoors or in an area in which other people are unlikely to breathe tobacco smoke. Because the hazards of passive smoking appear to be greatest for children younger than one year of age, this recommendation should be strongly reinforced for parents and those planning a pregnancy.

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Urinary Tract Infection in Geriatric Patients

THE INCREASING prevalence of significant bacteriuria with advancing age is of major concern to family physicians caring for geriatric patients. The rate is about 20% in the general ambulatory population aged 65 years and older and rises to 35% to 50% for those confined to hospitals. Possible reasons for this high prevalence in the elderly include obstructive uropathy, decrease of antimicrobial secretions from the prostatic gland, increased amounts of postvoiding residual urine due to prostatic hypertrophy and pelvic floor relaxation, fecal incontinence and soiling in women and a greater likelihood of indwelling catheterization.

The diagnosis of urinary tract infection in all age groups is based on quantitative urine cultures of clean-catch midstream specimens. A "positive" culture is one that grows 10^5 organisms or more per milliliter of urine. One clean-catch urine specimen has an 80% probability of being correctly identified as having significant bacteriuria. Two specimens growing the same organism have a 95% probability, while three specimens are nearly 100% accurate. Proper collection of the urine specimen depends on the individual patient and the adequacy of instructions. While the urine culture is considered the gold standard for diagnosing urinary tract infections, other tests are also available. These include routine urine analysis, Gram's staining, chemical analysis (leukocyte esterase and nitrite) and "dipslide" (Isocult or Uricult) of the urine. The results of these tests are subject to the same influences (urine concentration, collection, handling and preparation) as the urine culture, but have less sensitivity and specificity.

The most common infecting organisms are aerobic Gram-negative bacilli from the gut. *Escherichia coli* cause about 80% of urinary tract infections in the elderly. Another 10% to 15% of infections are caused by *Proteus, Klebsiella* and *Enterobacter* organisms; the remaining 5% to 10% are due to such pathogens as *Pseudomonas,* staphylococcal organisms and group D streptococci.

Urinary tract infections in the elderly may include the traditional symptoms of frequency, dysuria, hesitancy, urgency and nocturia. But acute confusional state, mental state changes or incontinence may also be the presenting complaints. Moreover, most of these infections in older adults are

asymptomatic. Because bacteriuria in older adults has been associated with an increased mortality rate, these diagnostic screening methods are of clinical importance.

The management of asymptomatic bacteriuria in the elderly is subject to debate and is under further investigation. Limited treatment trials with antibiotics for asymptomatic bacteriuria in geriatric patients have had high recurrence rates. On the other hand, any geriatric patient with symptomatic bacteriuria (bacteriuria and symptoms of infection) should be treated. Current treatment recommendations include 7 to 14 days of therapy with a safe, nontoxic, easily filtered drug such as the penicillins, cephalosporins, short-acting sulfonamides, tetracycline, trimethoprim or trimethoprim-sulfamethoxazole after the infectious agent is identified by urine culture. While single-dose and short-course antibiotic regimens have been therapeutically effective in healthy young women with uncomplicated lower urinary tract infections, this approach in the elderly has had unacceptably high rates of failure in recent studies. When bacteremia may be present, parenteral therapy with antibiotics such as aminoglycosides and cephalosporins should be used. After the pathogen is identified, the regimen can be changed to a safer appropriate drug. Elderly patients with structural abnormalities of the urinary tract, such as calculi, or chronic bacterial prostatitis may become reinfected, usually within one to two weeks. These patients who quickly relapse need to be evaluated further. If no structural abnormalities are found, then a three- to six-week course of therapy is recommended.

Long-term prophylactic therapy with trimethoprim (alone or in combination with sulfamethoxazole) for frequent symptomatic reinfection has been used successfully; urine cultures, however, should be done frequently and the antibiotic changed if bacteriuria recurs. Patients with indwelling catheters should have periodic urine cultures to identify the current infecting organism. Extended chemoprophylaxis for this group of patients does not prevent infection and risks drug-resistant sepsis.

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Assessing the Fetal-Placental Unit

MANY COMMON COMPLICATIONS of pregnancy, notably, gestational diabetes, pregnancy-induced hypertension and postmaturity, adversely affect the placenta and thereby place a fetus's ability to tolerate labor in jeopardy. Over the past two decades, numerous techniques have evolved for assessing the status of the fetal-placental unit; yet, until recently these techniques have often been costly, cumbersome and time-consuming.

Maternal urine or serum estriol determinations are sensitive predictors of fetal-placental function. Their appropriate use, however, requires serial determinations, often over a period of several days or weeks, and can incur considerable expense. Oxytocin contraction testing also is a reliable predictor of fetal-placental function, yet the need for intravenous administration of medication makes this process technically cumbersome. Non-stress testing, which has generally supplanted the oxytocin contraction testing as an initial screening device, is a reasonable predictor of fetal well-being but may less reliably predict fetal-placental function, particularly during the stress of labor. Maternal perception of fetal movement has long been recognized as an indicator of fetal well-being, and there have been recent efforts to develop fetal movement count protocols. Such counts are best used as a qualitative screening assessment with other more quantitative techniques used to more precisely assess fetal status.

Two more recently developed screening techniques appear to provide rapid and accurate assessment of fetal-placental function. Ultrasonic determination of amniotic fluid volume is one such technique. While the volume of amniotic fluid normally diminishes as the pregnancy approaches term, a finding of significant oligohydramnios is a specific predictor of poor placental function, particularly in a postmature pregnancy. It appears also that the presence of spontaneous fetal respirations detected on real-time ultrasound is predictive of fetal well-being.

Mammary self-stimulation contraction stress testing is a second new technique for assessing fetal-placental function. Breast self-stimulation can safely produce sufficient oxytocin secretion to stimulate contractions that satisfy standard criteria for a contraction-stress study. The test, effective in about 60% of women, is rapid—generally requiring less than half the time of a standard oxytocin contraction test—reliable and well accepted by patients.

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Tuberculosis in Nursing Homes

EVEN THOUGH the incidence of tuberculosis for all ages has declined yearly since before 1900, elderly persons now account for the largest proportion of tuberculosis cases of any age group. The predominance of cases in the elderly has been attributed to reactivation of previous infections that occurred when tuberculosis was much more prevalent. The high incidence in the elderly cannot be explained by the increase in the proportion of people in the population older than 65. Factors contributing to this problem include the delay of diagnosis due to atypical clinical presentations of reactivated infections and impaired immunologic responsiveness associated with advancing age and many chronic diseases.

Stead and co-workers have shown that newly acquired cases of tuberculosis can occur in nursing homes. There have been several reports of tuberculosis epidemics among residents of nursing homes, and the predisposing factor has been close living quarters that allows dissemination. Stead showed that in Arkansas 10% to 15% of persons newly admitted to

nursing homes reacted positively to a two-step tuberculin skin test, a rate much lower than expected for this age group. Among patients already living in nursing homes, the prevalence jumped to 20.8%, with a rate of conversion proportional to the duration of residence.

Tuberculosis control in nursing homes is based on the principles of surveillance and containment. Preadmission screening with tuberculin skin tests and chest roentgenograms is preferable. Tuberculin skin testing should be done using a two-step protocol because some patients whose skin tests are initially negative will subsequently react positively to a second skin test due to a "booster" immunologic response. The results of the first test are read at one week, with 10 mm induration or more considered positive. If negative at one week, another skin test is applied and read at 48 to 72 hours. If the chest roentgenograms are normal and the two-step tuberculin tests are negative on admission, a patient should be retested yearly using the two-step tuberculin test. For any resident in whom a chronic cough develops that is not explained by other acute illnesses, three early morning sputum specimens should be examined for *Mycobacterium tuberculosis*. Those who have converted from a negative to a positive skin test should have a chest roentgenogram and, if coughing, a sputum examination.

Stead showed that preventive therapy with isoniazid (INH) effectively decreases the incidence of active tuberculosis in nursing homes. Preventive therapy with isoniazid in a daily dosage of 300 mg should be considered for all patients whose skin tests are positive and who are without documented active disease or recent antituberculous drug therapy. The recommendation for duration of therapy is currently 6 to 12 months in compliant patients.

Elderly patients should be followed closely for signs and symptoms of isoniazid-induced hepatitis, and serum aspartate aminotransferase (AST, or SGOT) levels should be monitored before and periodically during treatment. If the AST level increases more than three to five times baseline levels, the isoniazid therapy should be discontinued. Patients receiving preventive therapy should also be followed for vitamin B_6 deficiency. As always, active cases of tuberculosis should be treated aggressively with multiple antituberculous drugs and the sputum checked periodically for *M tuberculosis*. Treatment of active cases should continue for at least six months.

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Crisis Precipitation in Alcoholism

ALCOHOL ABUSE continues to have a devastating effect on the health of millions of Americans. Any significant change in the morbidity and mortality of alcohol abuse will require more effective interventions earlier in the course of the disease. The greatest single barrier to earlier treatment is a patient's denial of the problem. Many alcohol treatment programs are adopting an innovative approach to break through this denial. The success of this innovative approach could be enhanced by the primary care physician's knowledge and participation.

Called either "intervention," "confrontation" or "crisis precipitation," this approach operates on the assumption that problem drinking continues as long as an alcohol abuser perceives more benefit from drinking than from abstinence. Rather than waiting for this perception to reverse when the patient hits "rock bottom," with all the attendant health risks, the intervention technique offers a person with alcoholism a powerful preview of "rock bottom" to compare with the caring and support of significant persons in his or her life. This approach works best when the index patient still has some intact, meaningful, positive relationships with people who recognize alcohol abuse as a problem for the patient. These people—family, personal physician, employer, minister and friends—carefully rehearse the "intervention" meeting with each other and an alcoholism counselor. The rehearsals are crucial to ensure that all concerned can confront the alcohol abuser with certainty, consistency, compassion and caring. The goal is to avoid criticism, blaming and coercion and to present treatment as an option that is chosen with dignity and self-respect.

When "rehearsals" are finished and all logistic barriers to beginning treatment have been considered, some pretext is arranged to get the alcoholic person to a place where all the key persons have assembled. Each person in turn discusses their perceptions of the patient's behavior when sober and when drinking. They describe the effect the person's drinking has on their life. They express their concern for the patient and why they want that person to seek treatment. Finally, they state the consequences of continued drinking. These must be clear and definite, not vague threats. For example, a wife must be certain of her choice if her husband continues drinking—separate bedrooms, separation or divorce; likewise the employer—probation, demotion, termination and so forth. All consequences must be tied to drinking behavior, not the emotions or judgments of the persons. All persons present must insist the problem drinker enter treatment immediately.

Evaluation of this technique must consider several factors. First, several studies have shown that any process that gets a person with alcoholism into treatment, such as voluntary admission, court-ordered commitments and the like, results in similar rates of abstinence. So if the intervention process gets people there before they might have otherwise, the benefit is in the decreased morbidity that might have occurred with any further delay. Second, no complications have been reported that would not have been expected in the natural history of the disease. Third, even if a patient does not seek treatment immediately after the meeting, the planned consequences provide continued, structured pressure on the patient and support for the family. Given those considerations, published and unpublished reports claim that about 70% of interventions will result in the alcohol abuser entering a treatment program. Overall, 55% to 60% of those patients will remain abstinent at least two years, with the abstinence rate rising to 80% if treatment was initiated while job and familial relationships were still viable.

Because a family physician often has a preexisting nonjudgmental rapport with the patient, he or she can play a valuable role in this process. The physician can diagnose the

alcohol abuse, identify the family members affected by it and often will be aware of other key persons in the patient's life. If individual office counseling is ineffective, the physician can inform the significant others of this technique and coordinate planning with a local alcohol treatment facility. Finally, by attending the intervention meeting, the physician can dramatically underscore the gravity of the physical effects of continued drinking and demonstrate the depth of the physician's concern for the patient. With more professional attention and systematic problem-solving of the personal, familial and social factors contributing to alcoholism, approaches like this can help reduce the widespread tragedy of this preventable health problem.

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Panic Disorder

PANIC DISORDER, commonly known as panic "attacks," is listed in *The Diagnostic and Statistical Manual of Mental Disorders*, third edition (DSM III), under "anxiety disorders." This disorder was described by Freud as early as 1895, and recent studies have provided new information. Panic disorder occurs in 4 to 12 people per 1,000 of the general population and occurs in women three times as often as in men. It usually begins in late adolescence or early adulthood, but may also begin in mid-adult life. It can be limited to several episodes or become a chronic condition.

Many patients with panic disorder, not attributing their symptoms to anxiety, present to their primary care physicians for evaluation. They describe sudden and unpredictable feelings of fear or terror accompanied by autonomic symptoms. Thoughts of dying or going crazy are often reported. Albeit infrequently, panic attacks can be triggered by certain stimuli. They usually resolve spontaneously within minutes, but have been known to last for hours. To meet DSM III criteria, there must be three panic attacks within a three-week period, not during extreme physical exertion or a life-threatening situation. Physical symptoms commonly reported during an attack include shortness of breath, chest pain, palpitations, tingling in the extremities, dizziness or faintness, sweating, hot or cold flushes and trembling.

Recent studies of patients with panic disorder have led to interesting insights into its pathophysiology, and there are some data that suggest a genetic transmission of this condition. Positron emission tomography has shown decreases in left to right parahippocampal blood flow and oxygen metabolic rates, indicating the possible role of noradrenergic or serotonergic central mediation. No demonstrable increase in the blood levels of β-endorphin, cortisol or lutcinizing hormone provides evidence against the theory that panic attacks are controlled by a pituitary-adrenal activation mechanism. Studies have shown that a variety of substances infused peripherally can precipitate a panic attack in patients who already have the condition, but not in normal controls. Imipramine hydrochloride, monoamine oxidase-inhibitors and alprazolam block these induced attacks.

The differential diagnosis should include medical and psychiatric disorders. Cardiovascular symptoms are reported most frequently. Although a causal association has not been proved, it was recently reported that 34% of patients with panic attacks also have a mitral valve prolapse. The possibility of alcohol or sedative withdrawal and caffeine or amphetamine intoxication should be investigated. In the differential diagnosis of other psychiatric conditions, major depression and agoraphobia should be considered.

Pharmacologic intervention has been proved effective when adequate dosages are given for sufficient lengths of time. Imipramine hydrochloride in dosages of 75 mg to 150 mg a day is generally the drug of choice, and other tricyclic antidepressants may also be effective. Alprazolam in divided dosages of 3 mg to 6 mg a day can be used, but one should begin with a lower dose and titrate it to a level that relieves the panic attacks. This is a new medication and may be associated with physical and psychological dependence. Phenelzine sulfate is not a first-line drug of choice and should be reserved for those instances wherein patients have failed to respond to the other medications. It can be used in dosages of 60 mg to 90 mg, but there are strict food and drug restrictions associated with its use. Once a medication has been successful in treating panic disorder, its use should be continued for about six months, then the dose slowly tapered, watching for recurrence of panic attacks.

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Estrogen-Progesterone Replacement at Menopause

WIDE ACCEPTANCE now exists for prescribing short-acting oral estrogens in the lowest effective dose for cyclic replacement in women entering menopause naturally or surgically. Indications are for maintaining bone mass and preventing osteoporosis, which accelerates at the climacteric without intervention. Estrogen replacement only (dependent on dosage) increases the risk of endometrial cancer fivefold. A dosage-response hepatitis rarely develops with the administration of estrogen. Yet, 1.2 million bone fractures a year happen to women older than 60 years who are not taking estrogen. The risk of death from hip fracture rises rapidly after the age 60 from 20% to as high as 50% at age 80. Each year more women die of preventable hip fractures than of all ovarian-endometrial cancers combined.

To avoid the endometrial hyperplasia for women with their uteruses intact and yet protect against the multiorgan symptoms of estrogen deficiency, the use of estrogen is now recommended to be combined with 10 to 13 days of progestin use in a cyclic manner similar to the physiologic pattern of a premenopausal woman. A typical protocol is 25 days per

month of 0.625 mg conjugated estrogen paired with 10 mg progesterone the last 10 to 13 days of the 25-day cycle. Some women will resume menses with this and will need endometrial sampling to assure there is no adenomatous hyperplasia. Progestin administration is probably indicated in women after a hysterectomy to protect the breast from unopposed estrogen for what will be the rest of a woman's life. The use of progesterone apparently increases the risk of cardiovascular disease, including hypertension, angina and coronary artery disease. The pattern of women at risk is poorly defined at this time but appears to be the same as for birth control pills—that is, smokers and a family history. The hepatic effect of oral estrogen use includes hypertension, cholelithiasis and intravascular clotting, which are lessened with low-dose cyclic usage and future newer estrogen analogs that are being researched. Women completing treatment for breast and other malignant lesions may still be candidates for estrogen replacement; an oncology consultation is recommended.

All women need dietary education to include calcium (1.0 grams per day to age 60, 1.5 grams thereafter), vitamin D (with sunshine during exercise), fluoride (1.0 ppm in water or 1.0 mg tablet per day) and exercise in their daily routine to minimize osteoporosis. It is also well established now that in postmenopausal women, low-dose, cyclically given estrogen added to this regimen will further minimize osteoporosis and in most instances is probably indicated. The more complex pharmacologic issues to be resolved are what type and how much estrogen and progesterone are best for overall health.

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Editorials

New Dimensions for the Art of Medicine

MUCH HAS BEEN WRITTEN and much has been said about the art of medicine. In the centuries and millennia before the present era of scientific medicine, the art loomed large in the practice armamentarium of physicians. Since the advent of modern medical science and patient care, the art has often been viewed as less important whether in medical education or patient care. Perhaps the time has come for a renaissance and to consider anew the role and dimensions of the art of medicine in today's patient care.

The art of medicine has always found its foremost expression in an interaction between a patient who is seeking help and a physician who seeks to give it. This is a very human interaction. In a narrow definition it has been described as the manner and behavior of a physician or other health care provider in delivering care to, and communicating with, a patient. This hardly seems an adequate definition or description. At the very least the art has always sought to win the trust and confidence of a patient in a physician's ability and willingness to help and at the same time to develop a willingness on the part of a patient to accept a treatment program recommended by the physician and then to comply with it. But, whatever the definition, the art of medicine is an intensely human affair and has always been a powerful tool in the relationship between a doctor and a patient. In recent years profound changes have occurred in medicine and society that are beginning to add new dimensions to this relationship and, with this, new dimensions to the art of medicine.

For one example, the role of a patient is changing. Physicians no longer give "orders" to patients without any particular explanation. Nor do patients always, or even almost always, obey the directions that are given. Moreover, it is becoming conventional wisdom in some quarters that it is not the doctor who should decide what to do but rather the patient, who must be informed and then allowed to make his or her own decision as to what will be done or not done. Questions arise. How much information should be given to a patient? How well does, or can, a patient comprehend the pros and cons of the alternatives presented? And then there is the legal doctrine of informed consent, vigorously upheld by the courts in recent years. How to decide what to do, and how and when to do it, in the new kinds of relationships that are coming to exist between doctors and patients is clearly the beginning of a new dimension of a physician's art.

Both physicians and patients now place great faith in medical science and modern technology. But it turns out that medical science is not always precise, although the technology may be more so. It is an arena full of probabilities and possibilities. There are few certainties, except that science and technologies are amoral and inhuman, and no two humans are ever biologically and experientially alike. So generalizations about humans or any groups of humans are risky when applied to any specific individual. The art, however, is a tool that can be applied intelligently and compassionately to help solve the individual problems of specific persons, using appropriate science and technology as indicated by professional judgment, always in the best interest of a particular patient who is served. And, conventional wisdom and informed consent notwithstanding, the fact is that many decisions in patient care are, and have to be, made unilaterally by physicians. All these judgments, whether scientific or compassionate and human, are, or should be, made in the realm of new and old dimensions of the art as well as of the science of medicine.

There are many other examples of emerging trends that are bringing other new dimensions to this age-old art. Some are particularly well known to practicing physicians who feel their impact almost every day and in almost every relationship with a patient. Among many of these the theme is conflict. When a patient does not have to pay the bill for care, the real payor has an interest that does not always match the interest of that patient. Physicians were always concerned with the cost of care when patients paid the bill, and now they must be concerned with the cost when others pay the bill. Then there are often conflicts of interest when scarce resources are to be used and paid for. Understandably, in all of this conflicts arise among physicians who prescribe care, patients who need care and those who pay for and administer it—these latter often with an imperative to reduce costs and increase profits. And then, there is the ever-present threat of professional liability, of an open conflict between doctor and patient in a court of law. The skillful juggling of potential conflicts such as these has clearly come to be another important dimension in the art of medicine.

Caring for patients in today's health-care environment all too often may seem to be something like a nightmare to many physicians. But looked at in another way, the challenge of these new dimensions of care and of the art of medicine can be exhilarating. The role of a practicing physician is actually coming to be something more akin to that of a conductor of a symphony whose art is to bring the many pieces of an orchestra into harmony to produce a good performance of a specific work. In similar fashion, a physician's art will be to conduct the orchestra of health care for a patient so that all the pieces of the art and science of medicine (including factors in the health-care environment) will harmonize as much as practicable, to render the best possible care for the needs of each particular patient. In a very real sense the physician is on the podium in patient care and is positioned better than anyone else to lead this orchestra of many pieces. It would seem to follow, then, that in today's health-care environment, the physician's art, or the art of medicine, will be to orchestrate all the components in the care of any given patient so that he or she will receive as harmonious, efficient and effective care as possible under the circumstances, whatever these may be.

Is not the art of medicine, defined in this way, now really one of today's greatest challenges to our professional tradition and to our individual personal commitment as physicians? A renaissance, and renewal, of the art of medicine in terms of today's social, economic and political dimensions of patient care is very much needed both in medical education and medical practice. This is surely an exciting and, yes, exhilarating opportunity for the medical profession. And for practicing physicians who look at it this way, it should be fun!

MSMW

Iron Depletion, Deficiency and Overload

FINCH AND CO-WORKERS elsewhere in this issue evaluate plasma ferritin as a diagnostic tool. Plasma ferritin concentration in normal subjects is proportional to the storage iron content of reticuloendothelial cells from which it is secreted. Ferritin in experimental animals is cleared rapidly from the plasma by the parenchymal cells of the liver. The widespread inclusion of serum iron measurement in automatic clinical chemistry panels has disclosed many patients with low or high values. Serum ferritin measurement is very helpful in the diagnosis of these abnormalities; its appropriate use well demonstrates the need for the judicious selection of laboratory tests and an understanding of both the normal and abnormal physiology affecting test results.

A subnormal ferritin concentration is highly specific for iron deficiency, though both hypothyroidism and ascorbic acid deficiency lower serum ferritin levels. However, the diagnostic subnormal concentration of serum ferritin found in patients with iron deficiency may be elevated into the normal range by a complicating disease. With rare exceptions (paroxysmal nocturnal hemoglobinuria), iron deficiency is the result of blood loss, usually gastrointestinal, sufficient to exhaust reticuloendothelial iron stores with resultant low serum ferritin values. Serum iron concentration is also low in patients with infection, inflammation and neoplastic disease but is associated with increased reticuloendothelial activity and serum ferritin levels. Measurement of serum ferritin levels has obviated the previously frequent need to examine the marrow aspirate for hemosiderin, absent in patients with iron deficiency and normal or increased with inflammation. Serial ferritin determinations are useful in the detection of negative iron balance of patients in a variety of circumstances: recurrent occult bleeding, malabsorption of iron following a gastric operation, long-term renal dialysis therapy and the donation of blood.

With the notable exception of primary hemochromatosis, ferritin concentration is a sensitive indicator of iron overload with poor specificity. Most high ferritin values are not associated with iron overload but with inflammation, infection, malignancy, tissue necrosis, hypermetabolism and liver disease. Serum iron values (transient elevation may occur with necrosis) and transferrin saturation, however, are low or normal in all of these conditions except liver disease. In the absence of liver disease, persistent elevation of both ferritin concentration and transferrin saturation is diagnostic of iron overload. When liver disease is present several questions arise. Is significant iron overload also present? If so, is the iron overload due to cirrhosis or is the iron overload primary with consequent hepatic damage and cirrhosis?

Iron overload is the common result of many disorders. Disability and death may occur through failure of the heart, endocrine organs and liver, as well as from carcinoma of the liver. Because timely appropriate therapy is always effective, with complete cure and even prevention in some patients, early correct diagnosis is important. Total body iron stores in humans are maintained normally within the range of 0.2 to 1.5 grams solely by appropriate adjustments of intestinal iron absorption because no excretory mechanisms exist. Iron overload may occur due to repeated parenteral administration of blood transfusions or iron therapy, or due to persistently increased absorption secondary to substantially increased dietary iron, prolonged oral administration of iron medication or chronic hemolytic anemia, especially with intramedullary hemolysis. Thalassemia is the most frequent cause of severe iron overload with high mortality. Increased absorption in patients with alcoholic cirrhosis is associated with hemolysis resulting from portal hypertension and splenomegaly and often a coexistent increased iron intake with European wines or, in Africa, Kaffir beer; absorption may be greatly increased following a portacaval shunt procedure. Persistent increased iron absorption also occurs as a genetic metabolic disorder, primary hemochromatosis, an inherited autosomal-recessive disease in which the gene is closely linked to the HLA-A locus on chromosome 6.[1]

ABBREVIATIONS USED IN TEXT

DTPA = diethylenetriaminepentacetic acid
SD = standard deviation

Primary hemochromatosis differs from all other causes of iron overload in that the increase of body iron initially occurs predominantly in parenchymal cells. Only late in the course of this genetic disorder, after the development of parenchymal injury and cirrhosis, does reticuloendothelial iron become distinctly increased.[1] Correspondingly, the serum ferritin concentration also becomes considerably increased (>700 μg per liter) only after a pronounced increase in iron stores to 10 grams or more with consequent development of hepatic fibrosis and cirrhosis.[2] This sequence of progressive parenchymal iron overload with subsequent development of cytotoxic cirrhosis is reversed in the secondary hemosiderosis of alcoholic cirrhosis in which the progression of hepatic cirrhosis leads to portal hypertension, splenomegaly, hemolysis, anemia, increased iron absorption and increased reticuloendothelial iron stores. Iron is initially predominant in Kupffer's cells in contrast to primary hemochromatosis with its initial striking increase of iron within hepatic parenchymal cells without significant increase of Kupffer's cell iron. In patients in the advanced stages of either alcoholic cirrhosis or primary hemochromatosis, iron is greatly increased in both Kupffer's cells and hepatocytes, and the liver biopsy specimens are frequently indistinguishable. Body iron stores, however, are much smaller in cases of advanced alcoholic cirrhosis than in advanced primary hemochromatosis in which the salient physical findings are hepatomegaly, splenomegaly, increased skin pigmentation, testicular atrophy, gynecomastia, loss of body hair and subchondral osteoarthropathy with bony swelling of metacarpophalangeal joints and involvement of the hip and shoulder joints. Signs and symptoms of diabetes mellitus may occur after progressive pancreatic hemosiderosis. Congestive heart failure and cardiac arrhythmias may result from progressive myocardial hemosiderosis.

Patients with secondary hemochromatosis have similar involvement of liver, spleen, skin and heart, with less frequent involvement of other organs and a substantial increase of hemosiderin in bone marrow reticuloendothelial cells. Only a moderate increase in marrow hemosiderin is usually observed in patients with primary hemochromatosis, strikingly less than the amount of hemosiderin in liver biopsy specimens.

The inclusion of serum iron measurement in routine clinical chemistry test panels has called earlier attention to many cases of hemosiderosis. Early diagnosis and appropriate therapeutic management can prevent organ injury and improve health. Serum iron levels may be elevated by hemolysis and hepatocellular damage and by increased body iron stores. In

patients with precirrhotic primary hemochromatosis, serum iron levels may remain normal for decades. Serum ferritin values remain normal or only borderline elevated in such patients, though they are a sensitive and fairly accurate measure of body iron stores in other patients without complications.[3] Though primary hemochromatosis is associated with certain human leukocyte antigens, particularly HLA-A3, B7 and B14, these are nonspecific and absent in a quarter of patients with primary hemochromatosis. Liver biopsy specimens furnish both morphologic information with qualitative assessment of iron content and distribution and quantitative measurement of tissue iron concentration.[4] Morphologic study is helpful in patients with precirrhosis but frequently no distinction can be found between alcoholic cirrhosis and the late stage of cirrhotic primary hemochromatosis.

Correlation of chemical analysis of hepatic biopsy tissue with total body iron mobilizable by serial venesection to iron deficiency shows a rough linear proportionality, providing an estimation of total body iron stores within ± 4.4 grams (2 standard deviations [SD]).[4] Measuring iron excretion in a 24-hour urine collection after intramuscular injection of deferoxamine provides a relatively gross indication of body stores. Measurement of total body iron chelatable by diethylenetriaminepentaacetic acid (DTPA) by measuring both iron and radioiron concentrations in a six-hour urine collection after intravenous injection of ^{59}Fe-DTPA provides a noninvasive and relatively accurate measurement of mobilizable storage iron. Correlation of total body DTPA-chelatable iron with total body iron mobilizable by serial venesection to iron deficiency shows a linear proportionality, providing an estimation of total body iron stores within ± 1.8 grams (2 SD) and 1.2 grams in the critical 0- to 10-gram range.[5,6] Accuracy is required in the 0- to 10-gram range because patients with alcoholic cirrhosis and secondary hemosiderosis rarely have more than 5 grams of iron, while cirrhosis rarely develops in patients with primary hemochromatosis until iron stores exceed 10 grams. The presence of more than 7 grams of iron in a patient who has not received multiple transfusions or prolonged parenteral or oral administration of iron and in whom increased dietary iron over a long term or chronic increased erythropoiesis (or both) are ruled out is diagnostic of primary hemochromatosis.

Early diagnosis of primary hemochromatosis in the precirrhotic stage prevents progression of disease when followed by appropriate venesection treatment and maintenance. Systemic venesection of 500 to 1,000 ml of whole blood per week until mild iron deficiency results usually will prevent or arrest development of the disease with striking symptomatic improvement. Measurement of DTPA-chelatable iron is noninvasive and both sensitive and specific for iron overload. In conjunction with the clinical history and other laboratory tests, the measurement can accurately differentiate various iron overload conditions and be a guide for both therapeutic venesection and maintenance prophylactic venesection. The DTPA chelation study can also identify those relatives of homozygous persons who also are homozygous and require prophylactic and maintenance venesection. Human leukocyte antigen typing of relatives identifies their risk while the DTPA iron chelation study identifies those in whom the risk has become a physical certainty. Simultaneously measuring both serum ferritin concentration and transferrin saturation is also useful in screening relatives of homozygous subjects.[2] Patients with secondary hemochromatosis require treatment of the primary condition. Venesection also is beneficial and can be implemented in all but patients requiring blood transfusion and patients who have intramedullary hemolysis and lack significant reticulocytosis.

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Needed Clout for Patient Advocacy

A RECENT DECISION by a California appellate court *(Lois J. Wickline v State of California)* has ruled that third party payors can be held liable for cost containment decisions that deprive patients of needed medical care. It goes on to warn physicians that they too may be held liable if they fail to protest when they comply, against their medical judgment, with the treatment limits imposed by third party payors.

The two parts of this decision, taken together, give substantial new clout to patient advocacy by physicians. First, physicians are encouraged to protest, and protest vigorously for the record, any third party decisions that deny care to a patient if, in the professional opinion of the attending physicians, the care is needed. Then, the ruling gives a new and potentially powerful incentive for a third party payor to seriously consider their action when one or more physicians do protest that what is being done to deny care to a patient is against their professional judgment. The payors are now put at risk as well as the physicians.

Patient advocacy by physicians has long suffered from a lack of clout in a world of health care that has become dominated by economic forces. If this appellate court decision is upheld, third party payors should have a new concern for what is happening to patients who are under their economic control, and a physician's duty to speak up for a patient's interest will be given additional and persuasive legal support. All of this should be healthy, and in patients' interests.

It is to be hoped that the effects of this decision will soon spread beyond the boundaries of California.

MSMW

Bentham in a Box—Technology Assessment and the Artificial Heart

JEREMY BENTHAM, the British genius who formulated the philosophical doctrine of utilitarianism, would have been delighted by modern technology assessment. In the late 18th century, Bentham proposed that personal and social life should be governed by a careful calculation of "utilities," the elements of human experience that produce a net balance of happiness over misery. By using a "felicific calculus," the greater happiness of the greater number could be achieved. Modern technology assessment is a variant on the "felicific

calculus," attempting to quantify harms and benefits with a view to pronouncing a technology "acceptable"—that is, effecting more good than harm. The artificial heart is an obvious candidate for technology assessment and elsewhere in this issue of the journal, Dr Van Citters describes one recent effort to evaluate mechanical circulatory support technology.

The good Bentham, who died in 1832, bequeathed his mummified body to University College, London. He still sits, dressed in his own clothes, in a glass box and is rolled out from time to time to join the dons for sherry. Bentham in his box is a shrunken and inert relic of his formerly powerful personality. He is, in this fashion, a metaphor for modern technology assessment. It, too, is confined in a box, limited in the scope and power that would make it a living force in society. The attempts to assess the artificial heart demonstrate this constricted capacity.

Technology, by definition, produces effects. Those effects are direct and multiple, immediate and distant. The combustion engine can cause a vehicle to move; it can also cause the congestion of a city and pollute its air. Technology assessment attempts to capture and calculate the direct and multiple, the immediate and distant effects. The determination of what effects to capture and how to calculate them is a theoretical problem of importance. Still, in recent years, many methods have been developed that go far toward resolving that problem. These methods allow, as one recent study states, "the acceptance, modification or rejection of technologies on a rational basis." The same study goes on to comment,

> that rationality, however, depends on many factors that go far beyond safety and efficacy, including economics, ethics, preferences of patients, education of physicians . . . the methods can take into account most of these factors, although combining the results from examination of different factors is a major task and one that is far from settled or solved.[1(p6)]

It is precisely the difficulty of combining these results that "boxes in" technology assessment. Certain of the crucial elements among the multiple effects and certain of the more distant effects seem beyond the range of calculation. This is not only because it is difficult to predict and to calculate, but because we seem, in principle, constrained from counting them into the assessment. When assessing medical technologies, such as the artificial heart, the most serious constraints are ethical: namely, our social commitment to an ethic of rescue and our social reluctance to count the costs of caring. These are, I rush to assert, laudable; we should rescue the endangered and we should generously care for the distressed. Indeed, our faults usually lie in carelessness and selfishness. Yet, these laudable commitments can obstruct our view of the real effects that they produce in the world. They exclude, a priori, certain elements from the felicific calculus and, thus, may lead to consequences that produce more misery than happiness.

The artificial heart is, as Van Citters explains, a rescue technology. It pulls back from the jaws of death a person whose heart is so damaged that its tissue no longer has the strength to pump blood. When Van Citter's National Heart, Lung and Blood Institute Working Group on Mechanical Circulatory Support (of which I was a member) sat down in the fall of 1983, one artificial heart had been implanted; before it completed its report a year later, the Humana series had begun.[2] In all of the reported cases, the patients were rescued from imminent death. Now, all are dead. None of those rescued persons lived anything like a normal life and several survivors suffered the ravages of serious cerebrovascular accidents. Should we continue the series in the effort to discover whether the rescue can be followed by renewed life? It is extremely difficult to answer no because our commitment to rescue compels us on: is not life of any quality better than death? Can we count the poor quality of rescued life against no life at all in our felicific calculus?

Also, if the artificial heart begins to prove itself, and one, and then another, patient leaves the hospital for a healthy 2.25 years at home (the Working Group's calculation of quality-adjusted survival with an implant), should we produce and implant as many devices as are called for? Should these devices be on the shelf, awaiting every patient who is brought to hospital suffering from massive myocardial infarction? The cost is large but not disproportionate to other major therapies. How can we be so callous as to count the costs of a technology so successful? Yet, should not the effects of this added cost on our health care system also be counted? Should we not wonder whether it might put pressure on other budgets for less dramatic health interventions? Should we not worry whether providing artificial hearts might compromise the provision of hypertension screening, of pacemakers, of antismoking education? What will be the social effect of permitting the wealthy to buy a new heart and the less wealthy to die? We seem reluctant to ask such questions in anything but the most rhetorical fashion because these questions imply that we are "costing out" caring.

This is technology assessment confined in a box. The longer effects in a person's life after rescue are excluded from consideration. "Quality of life," it is said, eannot be sufficiently quantified to be included in the felicific calculus. Yet, whatever else but quality of life is felicific? The broader effects of the new technology on other persons' lives, on other patients and on the health care system cannot be included. Yet, where has the concern for "the greater number" gone? These are the questions that technology assessment has difficulty combining into its rationality.

Bentham proposed a rational plan for the good life. His plan has many flaws and has been much criticized, yet its prospect for creating a humanly satisfying arrangement of social life intrigues us still. Even when we attempt to grasp the implications of a technology that he could not have dreamed of, the eccentric philosopher challenges us from his box. Could he speak, he would insist that we take into account the quality of life (he called it fecundity) and the social effects (in his term, remoteness) of the rescue technologies that our science makes possible.

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Case Reports

Magnetic Resonance Imaging of Cysticercosis

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ABBREVIATIONS USED IN TEXT

CT = computed tomography
MR = magnetic resonance
TR = repetition time
TE = echo-delay time

THE DIAGNOSIS OF CEREBRAL CYSTICERCOSIS is often quite challenging[1] both clinically and radiographically. Until recently, computed tomography (CT) was undoubtedly the imaging modality of choice for detecting these lesions. In this report, we describe the magnetic resonance (MR) findings in two patients with biopsy-proved cysticercosis and compare the results with those of CT.

Methods

Two patients were studied with a 0.5-tesla superconductive magnetic resonance imaging device manufactured by Picker International. Scans were generated in the sagittal, coronal and transaxial planes in both patients, and both T1- and T2-weighted sequences were used. The T2-weighted sequence comprised a repetition time (TR) of 2,200 ms and an echo-delay time (TE) of 80 ms, and the T1-weighted images were obtained using a TR of 850 ms and a TE of 40 ms. CT scans were available for review and comparison on both patients. In both cases, these were done on a GE 8800 CT scanner using 1-cm slice thickness.

Reports of Cases

Case 1

A 42-year-old Bolivian physician had her first generalized seizure in 1983. CT and angiography at that time were interpreted as normal. In August 1984, subcutaneous nodules developed on the patient's scalp, oral mucosa, neck and groin. A biopsy of the scalp and oral lesions was interpreted as being consistent with cysticercosis. Additional seizures occurred in November 1984, and a CT scan at that time showed areas of edema in both the right and left parietal lobes (Figure 1). MR imaging showed these lesions and several other areas of abnormally increased signal intensity on the T2-weighted images. They were located in the left and right parietal lobes, as well as in both temporal lobes and in the left frontal lobe (Figure 2). On the T2-weighted sequences, several of the lesions had small areas of decreased signal intensity lying eccentrically within the areas of increased signal intensity. Many of these areas were spherical and were felt to represent the scolex of the worm. Evaluation of the configuration of some of the lesions shows that those that are peripherally placed generally conform to the shape of cerebral sulci. Cysticerci within the subarachnoid space of the cerebral sulcus dilate the sulcus as the cysts enlarge. This may explain the somewhat unusual configuration and dimension of the lesions seen on these scans (Figures 2 and 3). The zones of increased signal intensity were felt to represent areas of edema and cyst formation. Following the magnetic resonance imaging, the patient was placed on a regimen of praziquantel for 14 days. A repeat MR imaging approximately three weeks later showed pronounced resolution of the edematous regions within the cerebral hemispheres (Figure 4).

Case 2

The patient, a 43-year-old man, experienced several episodes of numbness in the right arm lasting about 30 minutes. Following an episode of transient aphasia and seizures, he was admitted to hospital and a CT scan showed a rim-enhancing low-density lesion in the left frontoparietal area (Figure 5, left). Cerebral angiography revealed an avascular mass in the left parietal lobe. Results of a cerebrospinal fluid evaluation were normal. MR images showed an area of increased signal intensity in the left parietal lobe on the T2-weighted images. It was quite homogeneous in intensity on the section obtained directly through the midportion of the lesion, but a mixed pattern of signal intensity was observed just below the lesion, probably representing averaging of edema from the lesion and normal brain. Normal white matter structures were effaced, which was better seen on the coronal scan (Figure 5, middle and right).

About one week after the MR study, a posterior parietal craniotomy was done. A cystic lesion measuring approximately 2.5 cm in diameter was removed. Microscopic examination of hematoxylin-eosin-stained sections showed the typical cysticercus pattern of three characteristic layers: The outer cuticular and nuclear germinative, which comprise the tegument, and the parenchymatous reticular.

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The scolex was identified with its multiple hooks, indicating that this was a parenchymal cyst. A follow-up MR study showed reduced edema at the surgical site (not shown).

Discussion

Cysticercosis is a parasitic infection endemic to parts of Asia, India, Africa, Europe and Latin America. The causative organism is *Taenia solium,* the pork tapeworm. Humans are an intermediate host of the organism, acquiring it by accidentally ingesting tapeworm eggs from fecal-contaminated substances. The eggs hatch in the small intestine, burrow into the mucosa and then penetrate the venules. Mature larvae or cysticerci develop after 60 to 70 days.

Cerebral cysticerci may involve the brain parenchyma, ventricular system, subarachnoid space or a combination of these, which results in a variety of clinical manifestations. Symptoms usually do not appear for four to five years following infection by the organism; this latent period is related to the life span of the cysticercus. Viable cysts do not provoke an inflammatory reaction in the surrounding tissue, but dead larvae cause inflammation leading to an enlargement of the lesions and provocation of symptoms. The active cysts tend to assume the shape of the space they occupy and, therefore, may not be spherical or cylindrical when occurring in the ventricles or in the subarachnoid space. Dead cysticerci are usually partially or totally calcified spheres. When only partially calcified, there is usually a small, slightly eccentric calcification within the lesion, representing the calcified head, or scolex.

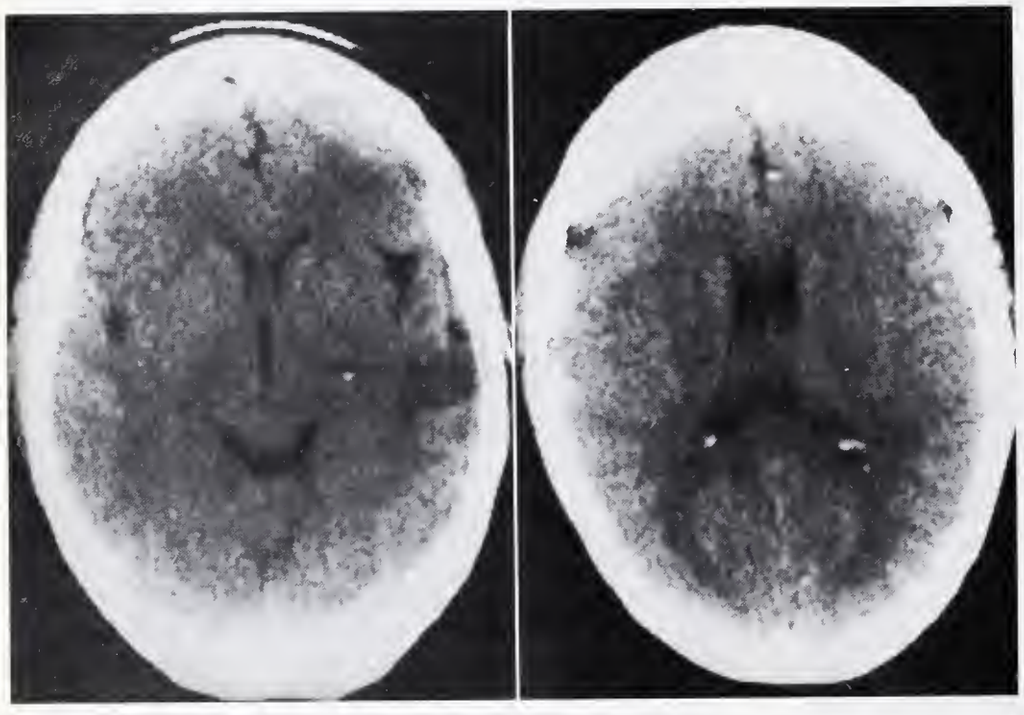

Figure 1.—Patient 1. Non-contrast computed tomographic scan showing edema in both parietal lobes **(left** and **right).** Additionally, a punctuate calcification with surrounding edema is seen in the left basal ganglia region **(left).**

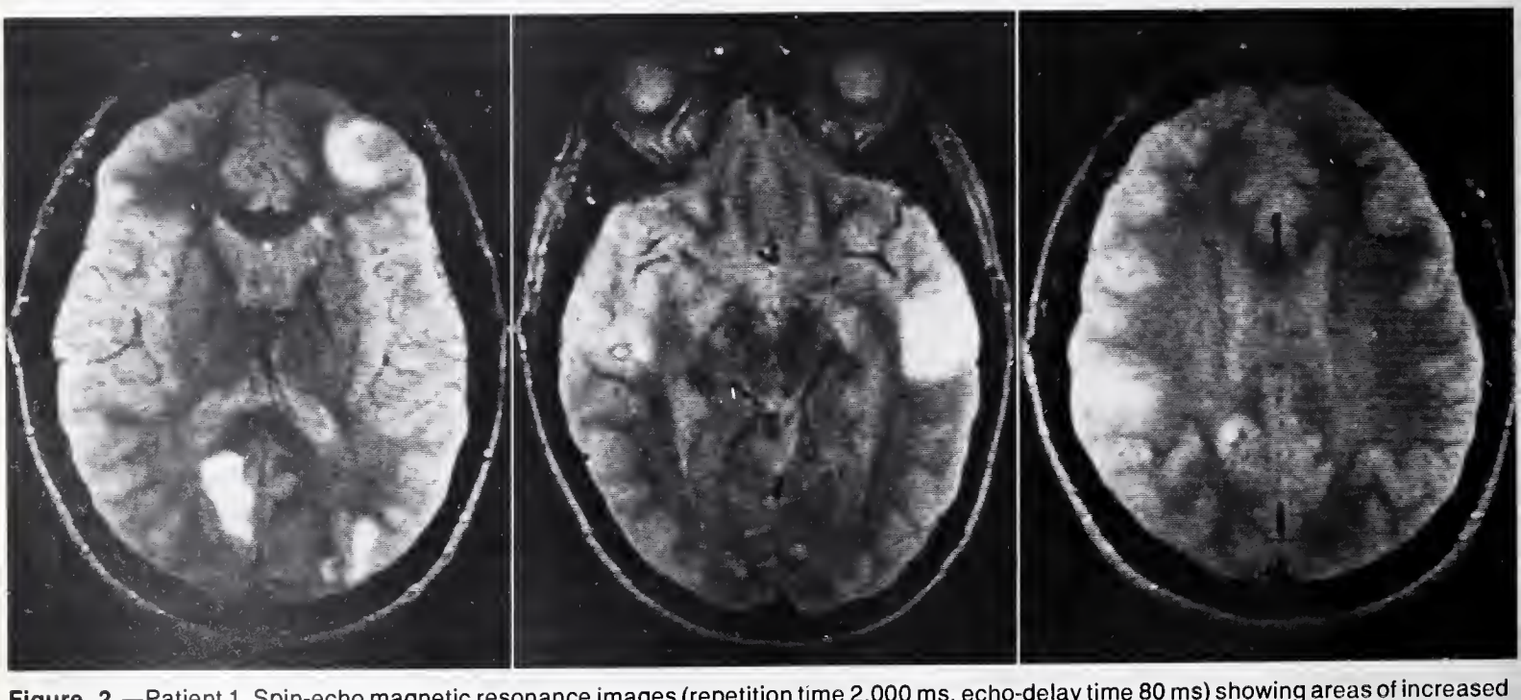

Figure 2.—Patient 1. Spin-echo magnetic resonance images (repetition time 2,000 ms, echo-delay time 80 ms) showing areas of increased intensity in the left frontal lobe **(left)** and bilaterally in the temporal **(middle)** and occipital lobes **(right).** Many more lesions are shown than with computed tomography (compare with Figure 1). Also, the borders of these high-intensity lesions conform to the shape of the surrounding sulci (see text).

The initial clinical presentation almost always includes seizures. Symptoms of increased intracranial pressure, meningitis or infarction can also be present. Results of a physical examination and cerebrospinal fluid evaluation are usually nonspecific. The diagnosis is made through the clinical history, serologic studies, imaging procedures and biopsy.[1]

The plain film, angiographic and CT findings of cysticercosis have been well described.[2-8] Before the advent of magnetic resonance imaging, CT was felt to be the diagnostic modality of choice.[1] CT findings include punctate calcifications, ring-enhancing cysts, ill-defined lucencies and round or oval homogeneously enhancing lesions. Calcifications are more commonly seen in adults, while diffusely enhancing lesions are more common in children.

MR was extremely valuable in evaluating cysticercosis in our two patients. Because of its higher sensitivity to increased water content, we feel that MR is more sensitive than CT in detecting the cystic lesions surrounded by edema. Indeed, in our first case, many more lesions were noted on MR images than on CT scans. The punctate areas of decreased intensity noted within the high-intensity signal most likely represent the scolex of the larva.[9]

Interestingly, in our second case, the cystic central area apparent on CT scan (Figure 5, left) is seen on MR images as an area of signal intensity similar to normal gray matter and much less intense than cerebrospinal fluid on the T2-weighted image (Figure 5, middle). This could possibly be due to a higher protein content within the cyst, facilitating spin-spin relaxation by the enclosed water molecules and thereby shortening the T2.[10] Perhaps the shorter T2 of these cysts will be a consistent finding that will increase the radiographic specificity of this diagnosis. (T1 and T2 are the spin-lattice and spin-spin relaxation times, respectively,

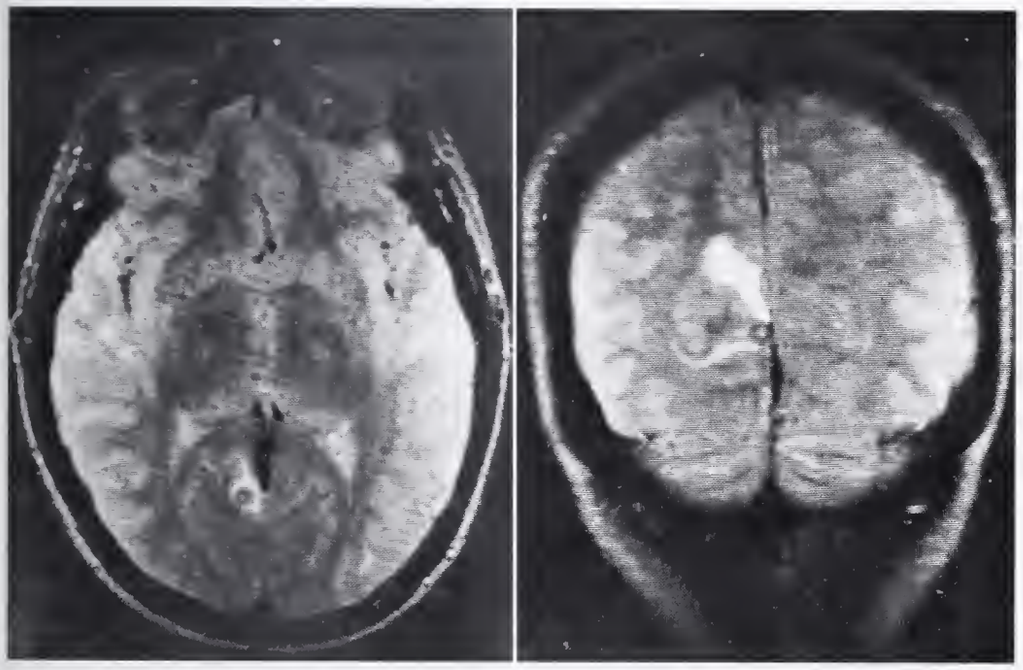

Figure 3.—Patient 1. **Left,** Axial (repetition time [TR] 2,000 ms, echo-delay time [TE] 80 ms) and **right,** coronal (TR 2,233 ms, TE 80 ms) spin-echo images through an occipital lesion. Note the focal spherical low-intensity area inferiorly within the high-intensity lesion in both images; this is felt to represent the scolex.

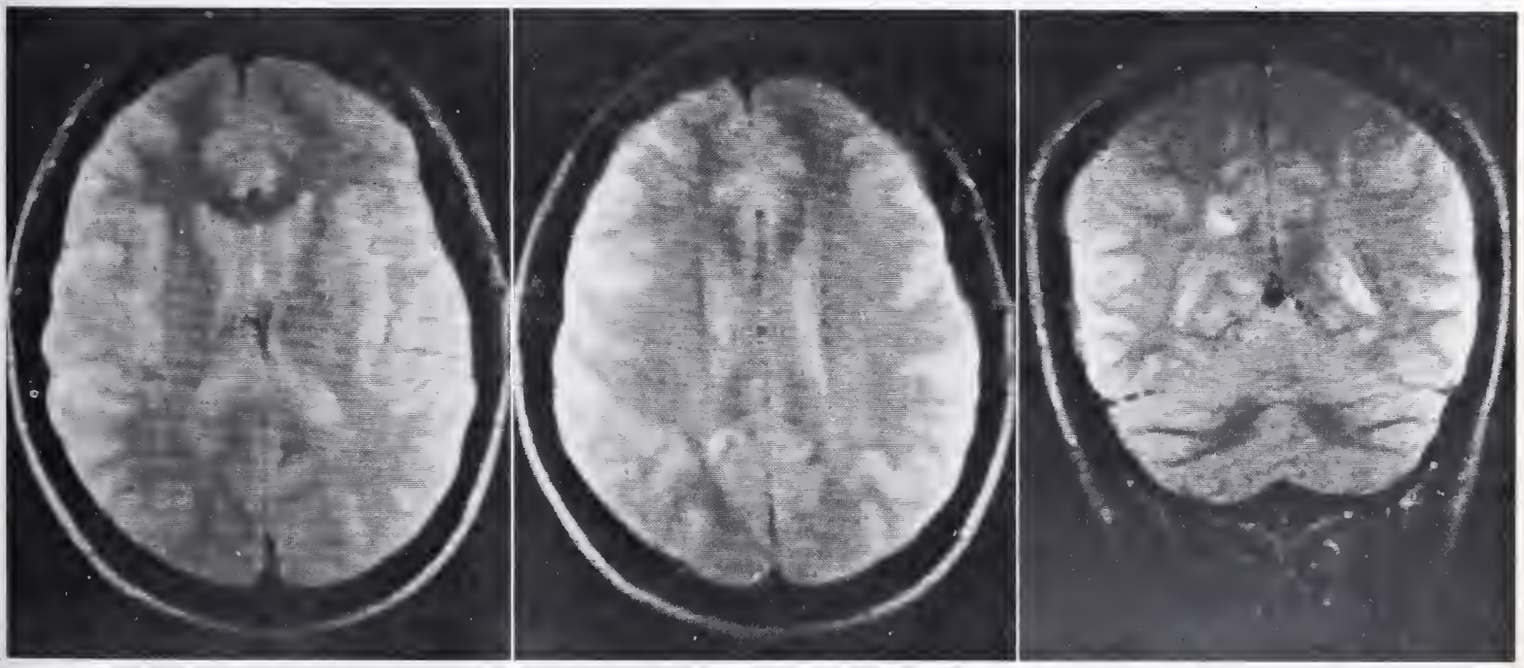

Figure 4.—Patient 1. Follow-up magnetic resonance images three weeks after beginning therapy with praziquantel. There has been pronounced resolution of the edematous regions within the cerebral hemispheres. The central low density **(right** and **middle)** is a machine artifact and not a lesion.

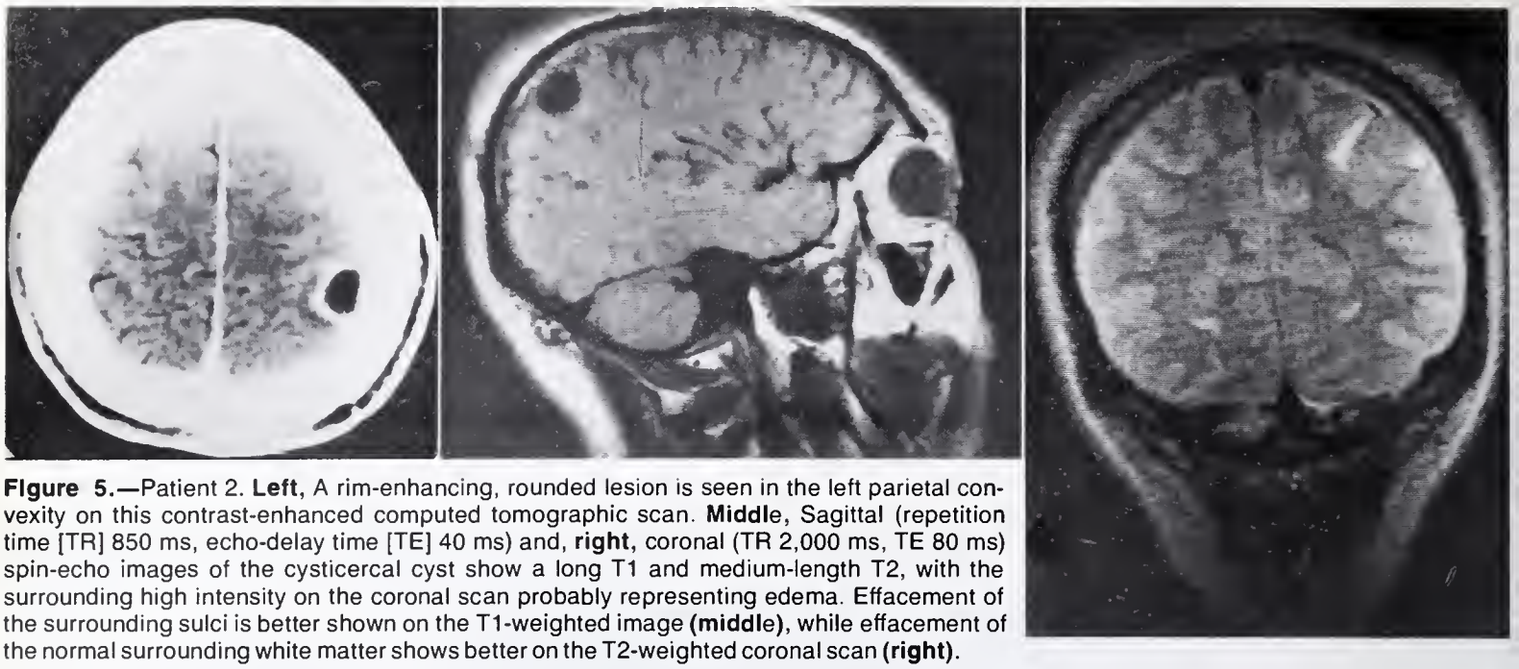

Figure 5.—Patient 2. **Left,** A rim-enhancing, rounded lesion is seen in the left parietal convexity on this contrast-enhanced computed tomographic scan. **Middle,** Sagittal (repetition time [TR] 850 ms, echo-delay time [TE] 40 ms) and, **right,** coronal (TR 2,000 ms, TE 80 ms) spin-echo images of the cysticercal cyst show a long T1 and medium-length T2, with the surrounding high intensity on the coronal scan probably representing edema. Effacement of the surrounding sulci is better shown on the T1-weighted image **(middle),** while effacement of the normal surrounding white matter shows better on the T2-weighted coronal scan **(right).**

for a nucleus in a magnetic field. They measure how quickly the nuclei return to their ground state energy level after excitation by a radio-frequency pulse. A short T1 relaxation time and a long T2 relaxation time are associated with high signal intensity on spin-echo sequences.[11])

The differential diagnosis in a patient with many long T1 and long T2 lesions in the brain includes multiple infarction (bland or septic), encephalitis subcorticalis chronica (Binswanger's disease), demyelinating disease and some metastases, as well as cysticercosis. The largely gray matter-subarachnoid space location of the lesions in our case would eliminate Binswanger's and demyelinating disease, and the clinical presentation should separate metastases and multiple infarcts from the presence of cysticercosis. Additionally, none of the above-mentioned diseases should present with a central, punctate, low-intensity focus.

Another feature that may be important in the lesions observed in our first case is their shape. As mentioned earlier, cysticerci tend to conform to the shape of the space they occupy when they are intraventricular or in the subarachnoid space. In case 1, the borders of the lesion tend to conform to those of the surrounding sulci. Unfortunately, no strongly T2-weighted imaging was done and, with the available images, it is not possible to separate cyst from surrounding edema. Possibly no cyst was present in these lesions, as none was seen on CT. If this is the case, we are probably just seeing edematous parenchyma. In future cases, additional spin-echo sequences will be used in an attempt to identify the cyst itself and determine its shape and T1 characteristics.

In our first case, follow-up MR imaging showed almost complete resolution of the lesions one month following therapy (Figure 4). Thus, another potential use for MR, especially in cases where the diagnosis is not completely firm, is to assure that appropriate response occurs following therapy.

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Hemophilus influenzae Pericarditis in Two Adults

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SERIOUS INFECTIONS caused by *Hemophilus influenzae* type b commonly occur during childhood. *H influenzae* has been recognized with increasing frequency in adults as a cause of

(Weingarten S, Weinberg H, Fang M, et al: *Hemophilus influenzae* pericarditis in two adults. West J Med 1986 Nov; 145:690-694)

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serious infections, including sinusitis, epiglottitis, bronchitis, pneumonia and, less commonly, meningitis, appendicitis, urogenital infections, cellulitis, cholecystitis, septic arthritis and endocarditis.[1] *H influenzae* pericarditis is uncommon; 15 cases of *H influenzae* pericarditis have been reported in adults, including two involving ampicillin-resistant strains.[2,3] We report two cases of *H influenzae* pericarditis, including one with pericardial empyema, in previously healthy adults.* Moreover, the first case describes identification of a β-lactamase-producing, ampicillin-resistant strain in a pregnant woman.

Reports of Cases

Case 1

The patient, a 37-year-old gravida 2, para 1, pregnant woman, was admitted because of one day of sore throat, right otalgia, nonproductive cough and anterior pleuritic chest pain. The patient had previously been in excellent health. There was no illness in the family or history of recent travel. She worked as a counselor for emotionally disturbed children who were about 8 years old; earaches and presumed ear infections had been common among them. Penicillin was given orally before admission. On admission, the blood pressure was 110/70 mm of mercury, heart rate 136 per minute, respiratory rate 28 per minute and temperature 37.8°C (100°F) by mouth. On physical examination she had slight pharyngeal erythema, right submandibular lymphadenopathy, crackles over the lower posterior thorax bilaterally and a fundal height of 32 cm, consistent with a 33-week gestation. The fetal heart rate was 170 per minute.

The leukocyte count was 18,800 per μl, with 22% neutrophils, 63% bands, 4% lymphocytes, 3% monocytes, 4% metamyelocytes and 4% myelocytes. A serum creatinine level and results of a urinalysis were normal. The admission chest radiograph showed a patchy left lower lobe interstitial infiltrate and a small right lower lobe infiltrate. The electrocardiogram revealed sinus tachycardia with a rate of 140 per minute. Gram's stain of a sputum specimen showed moderate polymorphonuclear leukocytes, Gram-positive cocci, Gram-negative cocci and Gram-negative rods. Blood cultures were done.

The patient was initially treated with ampicillin, 4 grams given intravenously per 24 hours, and subsequently erythromycin, 2 grams given intravenously per 24 hours, was added. Over the next 48 hours, the patient had increasing tachypnea and delirium and a metabolic acidosis developed. A repeat chest radiograph done 24 hours after admission showed small bilateral pleural effusions. On day 3, a thoracentesis of the left side of the chest yielded brown purulent fluid containing 215,000 leukocytes per μl, 99% of which were neutrophils. The fluid had a pH of 6.35, glucose 2 mg per dl, protein 3.6 grams per dl and lactic dehydrogenase (LDH) 2,898 units per liter. Gram's stain showed pleomorphic Gram-negative coccobacilli. A thoracentesis of the right side of the chest yielded similar findings. Bilateral closed chest tubes were placed and antibiotic therapy was changed to intravenous administration of ampicillin and gentamicin sulfate.

On cardiac monitoring the new onset of rapid atrial fibrillation was noted on day 4. A chest radiograph showed a newly enlarged cardiac silhouette and a two-dimensional echocardiogram revealed large anterior and posterior pericardial effusions. The patient underwent a left anterior thoracotomy and anterior pericardiectomy. Brown purulent pericardial fluid was obtained that had 168,000 leukocytes per μl with 90% neutrophils and a glucose concentration of 3 mg per dl, LDH 5,236 units per liter and protein 3.86 grams per dl. Gram's stain showed pleomorphic Gram-negative coccobacilli. A computed tomographic scan of the head and lumbar puncture showed no abnormalities. Cultures of blood and sputum specimens taken at admission and pleural and pericardial cultures grew *H influenzae* type b, biotype I, β-lactamase producing. Antibiotic therapy was changed to cefuroxime, 6 grams given intravenously per 24 hours. The patient temporarily required an endotracheal tube for acute respiratory failure. A serum immunoglobulin (Ig) G level was 347 mg per dl (normal 639 to 1,349) and IgA 47 mg per dl (normal 70 to 312). The patient was treated with a short course of γ globulin given intramuscularly. By the tenth hospital day, chest and endotracheal tubes were removed.

On the 14th hospital day, the patient gave birth to a 2,090-gram girl. There was no evidence of *H influenzae* infection in the baby or the placenta. Results of quantitative immunoglobulin studies done in the baby were normal. Results of repeat quantitative immunoglobulin studies of the patient during the convalescent period were normal, IgG level 1,190 mg per dl, IgA level 160 mg per dl and IgM level 209 mg per dl (normal 56 to 209). The patient and baby had an uneventual recovery.

Case 2

A 57-year-old woman was admitted because of dyspnea and a sore throat. She had previously been in excellent health. After her symptoms failed to improve on penicillin therapy given orally, she was admitted to hospital for further evaluation. On admission, the blood pressure was 100/70 mm of mercury, heart rate 112 per minute, respirations 48 per minute and temperature 35°C (95°F) by mouth. On physical examination she had pharyngeal erythema and thyromegaly. The leukocyte count was 14,400 per μl with 77% neutrophils, 13% lymphocytes and 10% monocytes. The admission chest radiograph showed bilateral infiltrates with pleural effusions. An electrocardiogram revealed a new right bundle branch block.

Initially the patient was treated with intravenous administration of erythromycin, nafcillin sodium and tobramycin. A thoracentesis was done and yielded 200 ml purulent fluid that contained 85,000 leukocytes per μl. The pH was 7.2 and a Gram's stain showed pleomorphic Gram-negative rods. Culture of pleural fluid grew *H influenzae*. Antibiotic therapy was changed to ampicillin and chloramphenicol given intravenously.

A repeat chest radiograph showed a globular cardiac silhouette. A repeat electrocardiogram revealed low-voltage, premature atrial contractions and ST-segment elevation consistent with pericarditis. A two-dimensional echocardiogram showed a moderate pericardial effusion. The patient had a new onset of atrial fibrillation, for which she was given digoxin and procainamide hydrochloride. She required an endotracheal tube for acute respiratory failure and administration of dopamine hydrochloride for hypotension.

*Marshall Kadner, MD, Stephen Uman, MD, and Bernard Axelrod, MD, gave permission to report these cases.

On the ninth hospital day, the patient underwent left thoracotomy and partial decortication. Her recovery was uneventful and three years later she remains in good health.

Comment

Purulent pericarditis is a serious disease with a fulminant course. The disease may be seen in association with pulmonary or intracardiac infection. Purulent pericarditis may also result from bacteremia or postoperative infection.[4] It occurs with increased frequency in debilitated patients, and fever, chills, night sweats and dyspnea are symptoms that usually accompany the infection. The mortality rate may be as high as 77%.[4] Organisms commonly associated include *Streptococcus pneumoniae, Streptococcus pyogenes* group A, *Staphylococcus aureus* and, less commonly, Gram-negative enteric organisms and fungi.[4,5]

H influenzae type b is an infrequent cause of purulent pericarditis in adults. The 15 previously reported cases of pericarditis associated with *H influenzae* are listed in Table 1. In only eight cases was the organism isolated from pericardial fluid. The ages of the 15 patients ranged from 18 to 60 years; ten were female. Most were previously healthy adults who presented initially with upper respiratory tract signs and symptoms. Ten patients presented with a sore throat, and ten had pneumonia or empyema associated with the pericarditis. Only one patient had *H influenzae* pericarditis without evidence of concurrent infection elsewhere. Blood cultures grew *H influenzae* in ten cases. All but three patients underwent pericardial drainage. There was evidence suggestive of *H influenzae* infection on Gram's stain of sputum, pleural or pericardial fluid in eight patients before bacteriologic confirmation. Two cases of ampicillin-resistant *H influenzae* purulent pericarditis were reported, with one shown to involve a β-lactamase-producing strain.[2] The mortality rate from *H influenzae* purulent pericarditis is significantly less than what is reported overall for purulent pericarditis.[4,5] Only 2 of 15 patients died of the illness. One death was related to sulfonamide-induced thrombocytopenia.[6]

The two patients presented here share many characteristics with previously reported cases. Both patients were previously healthy and presented with a severe sore throat and lower respiratory tract symptoms followed by clinical deterioration. The first patient, in particular, had early clinical features typical of adults with humoral immune deficiency in whom segmental pulmonary parenchymal disease develops.[16] Both patients were noted first to have *H influenzae* pneumonia and thoracic empyema. Purulent pericarditis ensued, most likely by continuous spread, although hematogenous spread cannot be excluded. In the first case, β-lactamase-producing *H influenzae* was cultured from the pericardial fluid.

In both cases, interpretation of the Gram's stain may have led to an early diagnosis of *H influenzae* infection before bacteriologic confirmation. A sputum Gram's stain was characteristic in 23% to 75% of adults with *H influenzae* pneumonia and bacteremia and in 71% of adults with nonbacteremic *H influenzae* pneumonia in previously reported series.[17,18]

H influenzae was once uniformly susceptible to ampicillin. Since the initial reports of ampicillin resistance in 1974[19] and then chloramphenicol resistance,[20] antibiotic resistance has become an increasing problem in treating cases of systemic bacterial infections. The prevalence of ampicillin resistance among *H influenzae* pediatric meningitis organisms rose from 19% in 1978 to 25% of the organisms reported more recently nationally with wide geographic variation.[21] The rates of resistance are lower in organisms identified from the respiratory tract. Resistance to chloramphenicol, especially among *H influenzae* type b bacilli, has remained low, with a rate of less than 1% in the United States.[22] A recent report from Spain noted that 41 of 225 strains of *H influenzae* were resistant to both ampicillin and chloramphenicol.[23] There is anecdotal experience with combined ampicillin and chloramphenicol resistance that is plasmid-borne in US isolates. At our hospital, currently 10% of *H influenzae* organisms are resistant to ampicillin, whereas no chloramphenicol-resistant organisms have been noted (M. A. Morgan, MD, unpublished data, Jan to Dec 1985).

Resistance to ampicillin in *H influenzae* is principally governed by the plasmid-mediated production of the triethylenemelamine β-lactamase enzyme[24] and, to a lesser degree, intrinsic resistance. Plasmid-mediated resistance to chloramphenicol is conferred via the production of chloramphenicol acetyltransferase. Another mechanism for ampicillin resistance is non-β-lactamase-mediated resistance due to alterations in penicillin-binding membrane proteins.[25] Additional factors implicated with antibiotic resistance include the following: previous β-lactam antibiotic therapy, geographic location and serotypes a to f (capsular antigen) and biotypes I to V classification.[26]

The initial choice of antimicrobial therapy is crucial in treating systemic infection in *H influenzae* and must include consideration of possible resistance. Antibiotic susceptibility testing and β-lactamase screening of all *H influenzae* organisms should be determined rapidly to guide subsequent appropriate therapy. One recommendation is that all cases of possible systemic infections due to *H influenzae* should initially be treated with chloramphenicol given intravenously at doses of 75 to 100 mg per kg every six hours (total maximum daily dose 4 to 6 grams a day) plus the addition of ampicillin at a dose of 150 mg per kg per day. If the organism is shown to be susceptible to ampicillin, the chloramphenicol regimen may be discontinued. The appropriate duration of antibiotic therapy depends on the site and extent of disease. The introduction of new cephalosporin antibiotics that penetrate cerebrospinal fluid, such as cefuroxime, cefotaxime sodium, moxalactam disodium, ceftizoxime sodium, ceftazidime, that have documented efficacy in the treatment of *H influenzae* systemic infections, including meningitis, offers possible advantages over either brief or prolonged courses of chloramphenicol therapy. Cefuroxime and selected "second"- and "third"-generation cephalosporins appear to be promising alternatives to chloramphenicol in treating life-threatening infections where β-lactamase-positive organisms are known or suspected.[27,28] The major drawbacks of these newer cephalosporins are the expense of some of the agents, the need to use ampicillin with them initially in empirical therapy for meningitis if *Listeria monocytogenes* or group B streptococci are considerations and the theoretic potential for the development of further *H influenzae* resistance.

The first case dealt with *H influenzae* type b, β-lactamase producing, in a pregnant patient who responded rapidly to the administration of cefuroxime. Chloramphenicol therapy was

TABLE 1.—Hemophilus Influenzae *Purulent Pericarditis in Adults*

Reference	Patient	Age (Years)	Sex	Symptoms	Ampicillin Resistance	Associated Infections	Positive Gram's Stain	Positive Cultures	Antimicrobial Treatment	Surgery	Outcome
Hensler, 1955[6]	1	24	♀	Cough, dyspnea and abdominal pain	...	Pneumonia and empyema	...	Pericardial fluid	Penicillin, sulfonamide, tetracycline	Pericardiotomy	Died
Crossley et al, 1973[7]	2	38	♀	Sore throat and chest pain	...	Pneumonia	Pleural and pericardial fluid	Blood, sputum, pleural and pericardial fluid	Cephalothin sodium, ampicillin, streptomycin	Pericardiectomy	Lived
Crossley et al, 1973[7]	3	44	♂	Sore throat and delirium	...	Pneumonia	Pleural fluid	Blood, throat and sputum	Ampicillin, kanamycin sulfate, chloramphenicol	Pericardiectomy	Lived
Duke and Donovan, 1973[3]	4	33	♀	Sore throat and neck tenderness	Yes	Pharyngitis	...	Pericardial fluid	Penicillin, cephalothin, ampicillin, chloramphenicol, dimethylchlor-tetracycline	Pericardiectomy	Lived
Alsever et al, 1974[8]	5	26	♀	Sore throat, fever, dysphagia and hoarseness	...	Thyroiditis, pneumonia, and empyema	Pleural and pericardial fluid	Blood, pleural and pericardial fluid	Cephalothin, chloramphenicol, ampicillin	Pericardiectomy	Lived
Rubin and Mollering, 1975[4]; Jafari et al, 1976[9]; Sink et al, 1982[10]	6	26	♀	...	...	Meningitis and upper respiratory tract infection	...	Pericardial fluid and blood	Chloramphenicol	Pericardiectomy	Lived
Jafari et al, 1976[9]	7	23	♀	Sore throat, vomiting, dyspnea and dysphagia	...	Empyema	Pericardial fluid	Pericardial and pleural fluid	Chloramphenicol	Pericardiectomy	Lived
Sink et al, 1982[10]	8	27	♂	Chest pain and dyspnea	...	None	Pericardial fluid	Pericardial fluid	Cefamandole, tobramycin, ampicillin	Pericardiectomy	Lived
Jennings et al, 1983[11]	9	59	♂	Chills and dyspnea	...	Pneumonia	Sputum and pericardial fluid	Blood and sputum	Tobramycin, penicillin, cefamandole, ampicillin	Pericardiectomy	Lived
Buckingham et al, 1983[12]	10	42	♀	Myalgias, sore throat, headache and neck stiffness	...	Pneumonia and meningitis	Pericardial fluid	Blood, sputum and pericardial fluid	Erythromycin, ampicillin	Pericardiectomy	Lived
Graham et al, 1983[13]	11	18	♂	Sore throat, chest pain and fever	...	Pneumonia	...	Blood	Gentamicin sulfate, cefazolin, ampicillin	None	Lived
Graham et al, 1983[13]	12	33	♂	Cough and chest pain	...	Pneumonia	...	Sputum and blood	Penicillin, oxacillin sodium, ampicillin	None	Lived
Mier and Shanson, 1984[2]	13	26	♀	Sore throat and swollen neck	β-Lactamase producing	Epiglottitis	...	Blood	Floxacillin, ampicillin, chloramphenicol	Pericardiectomy	Lived
Kiefaber et al, 1984[14]	14	31	♀	Sore throat and myalgias	...	Pneumonia	Pleural fluid	Pleural fluid and blood	Penicillin, ampicillin, chloramphenicol	Pericardiocentesis	Lived
Shiekh et al, 1981[15]	15	60	♀	Sore throat	...	Pharyngitis	...	Blood	...	None	Died
This report		37	♀	Sore throat, ear pain and chest pain	β-Lactamase producing	Empyema	Pleural and pericardial fluid	Blood, sputum, pleural and pericardial fluid	Ampicillin, erythromycin, cefuroxime, gentamicin	Pericardiectomy	Lived
This report		57	♀	Sore throat and dyspnea	...	Empyema	Pleural fluid	Pleural fluid	Erythromycin, nafcillin, tobramycin, ampicillin, chloramphenicol	None	Lived

avoided in this patient because of possible adverse effects on the fetus.[29] Biotype I of *H influenzae* identified from patient 1 has been described as more common than other biotypes in respiratory tract infections, although ampicillin resistance was not common in one study of biotype I organisms.[30]

An important complication of pericarditis is cardiac tamponade. Timely drainage either by surgical intervention or by means of repeated pericardiocentesis or catheter drainage is usually required for *H influenzae* pericarditis. Anterior interphrenic pericardiectomy has recently been recommended for drainage and prevention of constrictive pericarditis.[31] The patient in case 1 underwent pericardiectomy and had pronounced hemodynamic improvement following the procedure. Remarkably, our second patient and two previously reported patients had an uneventful recovery from their illness without drainage. None of these cases, however, had cultural confirmation of *H influenzae* purulent pericarditis. Aggressive diagnostic techniques and a drainage procedure are still recommended.

Although *H influenzae* is a rare cause of pericarditis in adults, it should be particularly considered in any patient presenting with an antecedent history of upper respiratory tract symptoms and a concurrent pneumonia, particularly with an associated empyema. Gram's stain of the sputum, pleural fluid or pericardial fluid (or all three) will often provide the diagnosis before culture confirmation; the use of counterimmunoelectrophoresis is another consideration. The prognosis is good with a combined approach of appropriate antimicrobial therapy that initially takes into account the prospect of bacterial resistance and adequate surgical drainage.

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Treatment of Cranial Osteomyelitis From Disseminated Coccidioidomycosis

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Coccidioidomycosis has been recognized for less than 100 years with as many as 100,000 cases occurring yearly in the United States. The fungus is acquired by the respiratory route and usually causes only asymptomatic infection found by skin test conversion. It is estimated to account for 70 deaths annually.[1]

The fungus is endemic to areas of the southwestern United States and Central and South America. Within the past four decades studies have suggested the incidence and severity of infection is related to race,[2,3] immune competence,[4] pregnancy[5] and age.[3] Blacks and Filipinos, patients with defects of immune competence, pregnant women and persons at either extreme of age seem more likely to have development of the infection and complications associated with dissemination.

Report of a Case

This 13-month-old black male child was in good health until 10 months of age when a slowly enlarging subcutaneous mass developed in the right maxillary region and in the right foot. The child was a military dependent whose family had recently been stationed in the San Joaquin area of California.

(Gillespie R: Treatment of cranial osteomyelitis from disseminated coccidioidomycosis. West J Med 1986 Nov; 145:694-697)

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There was no history of respiratory problems, skin rash or other systemic complaints. The child's growth and development were normal.

On physical examination on admission August 1983, he had a low-grade fever; a nontender, firm, 2- by 2-cm subcutaneous mass just inferior and lateral to the right orbit (Figure 1), and a diffuse, nontender, nonerythematous swelling in the right first metatarsal region.

Initial laboratory studies showed a leukocyte count of 30,000 per μl with a hematocrit of 29% and Westergren sedimentation rate of 140 mm per hour. A chest x-ray film and results of a urinalysis were normal. Coccidioidin and spherulin skin tests were negative, as were purified protein derivative, *Trichophyton* and *Candida* skin tests. A serum coccidioidal complement-fixation antibody titer was 1:256. A bone scan showed areas of diffuse uptake throughout the calvarium and the right first metatarsal. Skull x-ray films and a computed tomographic scan showed the soft tissue mass lateral to the right orbit and several confluent lytic lesions in the calvarium in both frontoparietal regions (Figures 1 and 2). Radiographs of the right foot showed changes consistent with osteomyelitis (Figure 3).

A biopsy specimen of the maxillary mass showed granuloma with spherules consistent with coccidioidomycosis. A regimen of amphotericin B was started that was administered for a total dose of 1 gram. Following institution of amphotericin therapy, more severe fevers developed that may have been related to use of the medication. Despite amphotericin therapy, the disease continued its relentless progression with worsening of the lesions seen on skull x-ray films, increased soft tissue swelling around the right orbit and right foot and new swelling in both frontoparietal regions.

Because of the lack of response to medication and persistence of the patient's anergic state, neurologic and orthopedic surgeons were asked to consider debriding the focal areas of bony involvement. On December 8, 1983, the child underwent debridement of the right foot lesion and a bifrontal approach to the cranial lesions.

At the operation the scalp flap was greatly swollen due to diffuse fungal cellulitis. Focal areas of calvarial erosion and granuloma formation were debrided with resection of bone extending into the right sphenoid wing and lateral orbital wall.

Figure 1.—A computed tomographic scan shows coccidioidal granuloma in the right periorbital region **(arrow)** with rarefaction of the sphenoid.

Figure 2.—A computed tomographic scan shows bilateral frontoparietal bone erosion and soft tissue swelling.

Figure 3.—Erosion and lytic and hypertrophic changes are noted in the right first metatarsal.

The patient's condition worsened postoperatively. Oral administration of ketoconazole, 100 mg, was begun in early January with gradually increased dosage to 200 mg a day. Skull and foot x-ray films showed progression of the bony involvement, and debridement of the right foot lesion was repeated. The most prominent area of involvement still appeared to be the calvarium, with skull x-ray films now showing evidence of total calvarial involvement with pronounced soft tissue swelling and edema of the entire scalp. Repeat skin tests remained negative and the serum complement-fixation antibody titer fell to 1:16. This fall in titer was unexpected and suggests suppression of the humoral immune system as this titer was done in the context of clinical deterioration usually associated with rising titers.

The patient underwent an operation on January 20, 1984, with a radical resection of the anterior half of the calvarium down to the base of the skull (Figure 4). In view of the patient's lack of response to earlier treatment, as thorough a debridement as possible was carried out to decrease the number of organisms challenging the patient's immune system.

Postoperatively a plastic helmet was fashioned to protect the areas where calvarium was resected. Ketoconazole therapy was discontinued and a regimen of itraconazole was started. The patient's immune function began to show evidence of improvement following the operation, with skin test reactivity to coccidioidin 1:100 on January 30, 1984. Follow-up skull x-ray films showed no further progression of bony erosion and the swelling of the scalp resolved. Antifungal therapy with itraconazole was continued and the patient was discharged.

Skull x-ray films on outpatient follow-up six months later showed substantial reconstitution of the previously resected calvarium with resolution of radiographic evidence of osteomyelitis in the nonresected bone. The coccidioidin skin test remained positive and coccidioidal complement-fixation antibody titers remained at 1:16. Over the next six months the skull reformed (Figure 5), there was no cosmetic deformity noted and the patient was asymptomatic. Outpatient therapy with itraconazole is continued on a long-term basis.

Figure 4.—A postoperative skull x-ray film shows the large area of infected bone removed at operation.

Discussion

Symptomatic persons with coccidioidomycosis usually present with cough, fever, malaise and pleuritic chest pains. Erythema nodosum occurs in 15% as a reflection of hypersensitivity to *Coccidioides immitis* and may be associated with a lower incidence of disseminated disease.[4] Failure of immune defenses to control the disease can lead to chronic pneumonia, miliary pulmonary coccidioidomycosis, pulmonary cavitation and extrapulmonary dissemination to skin, meninges, gastrointestinal and genitourinary tract, joints, liver and bone.

A diagnosis in asymptomatic patients often depends on positive coccidioidin and spherulin skin tests. In patients with disseminated disease, skin test reactivity often is absent, and, most commonly, complement-fixation titers increase with progression of the disease. In our patient clinical deterioration postoperatively was associated with a fall in titer, which is an unexpected occurrence. This may be related to the patient's young age or a suppressive effect of the large number of organisms on the patient's humoral immune system (or both). After the second more radical surgical debridement, evidence of a cellular immune response returned with the positive skin test reactivity. The persistence of a low complement-fixation titer at 1:16 would be consistent with the patient's clinical improvement.

Disseminated coccidioidomycosis may not be associated with pulmonary symptoms or changes on x-ray films. The diagnosis then rests on finding the fungus in specimens of urine, blood, biopsy or aspirate and an environmental history of exposure to an endemic area.

The role of host immunity in controlling the infection is becoming better defined,[6] and in our patient the disease progressed relentlessly until host immunity was reestablished.

In a recent series of 112 cases of coccidioidal osteomy-

Figure 5.—A skull x-ray film shows reconstitution of resected calvarium and resolution of radiographic signs of osteomyelitis.

elitis, the skull was found to be involved in 13% of cases.[7] This involvement usually takes the form of small cystic areas of bone destruction and poses a significant risk of meningeal spread, which is found in as many as 50% of patients with disseminated disease, often as the only manifestation of coccidioidal infection.[8,9]

The possibility that an infection may overwhelm the host immune system with resulting immunologic nonreactivity to the infecting organism is suggested by the return of an immune response in our patient after decreasing the antigen load by extensive debridement. Recent trials using levamisole hydrochloride are also directed at influencing the host-parasite immunologic interaction by dynamically influencing host defenses.[10] We were prepared to start this treatment if our patient's immune response did not improve following the second debridement.

The improvement of cell-mediated immune responses with treatment has been noted by others.[4,11] In our patient the rapid regrowth of calvarium in the infected area and control of the infection coincided with the return of cellular immune competence as evidenced by positive skin tests. This suggests that the immune defect may be due to the infecting organism itself and offers theoretic justification for aggressively debriding infected areas and administering chemotherapy as a means of improving a patient's immune status by reducing the antigen load.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Diagnosis of Organophosphate Poisoning

TO THE EDITOR: The diagnosis of mild to moderate organophosphate poisoning can be unequivocal in cases in which one does not have basic cholinesterase values. Midtling and colleagues described in this journal a novel diagnostic approach.[1] They had conducted a back-extrapolation of cholinesterase values to the time of poisoning. Similar cases were recently reported elsewhere.[2]

This method, although very helpful, cannot assist in the diagnosis of acute cases. Therefore, we suggest another simple method of diagnosing organophosphate poisoning: a blood specimen should be drawn for cholinesterase determination on admission of the patient, before and a few minutes after administration of an oxime (such as pralidoxime chloride). An apparent increase of cholinesterase activity after the administration will disclose the diagnosis of organophosphate poisoning, even if the initial levels are within normal limits.

In case oxime therapy has already been given before admission to the emergency room, a comparison should be made between erythrocyte and plasma cholinesterase activity. A markedly decreased cholinesterase activity in the plasma along with normal or near-normal erythrocyte cholinesterase activity will raise the possibility of oxime-treated organophosphate intoxication, since oxime-induced reactivation is much more rapid in erythrocytes than in plasma. This is true in most cases, except for rare cases of decreased plasma cholinesterase activity from other causes.[3]

This reactivation of cholinesterase by oximes is usually possible for a few days following organophosphate intoxications, after which aging of the enzyme occurs. Time for aging varies among various types of organophosphate.

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Catheter-Related Septic Thrombosis

TO THE EDITOR: In their recent review of catheter-related septic central venous thrombosis, Kaufman and co-workers identified 37 previously reported cases that were diagnosed antemortem.[1]

To this number might be added some of the 54 cases reported by Pruitt and colleagues[2] in a reference not cited by Kaufman. In at least 22 of these cases the diagnosis apparently was made antemortem.

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Scuba Diver's Thigh

TO THE EDITOR: Meralgia paresthetica usually is due to compression of the lateral femoral cutaneous nerve at the anterior superior iliac spine. The classical cause is an expanding abdomen secondary to ascites, obesity and pregnancy, but other mechanisms have been described.[1] These include stretching of the nerve by pelvic tilt or standing at attention for long intervals and injury from tight pants,[2] corsets, trusses, a heavy wallet,[3] tourniquets on the thigh[4] and a parachute harness strapped over the groin.[5] Recently we noted a previously unreported cause associated with participation in a popular sport, namely, scuba diving. This case should be of interest to readers and physicians in California who might encounter similar patients.

A 26-year-old woman was scuba diving for approximately 50 minutes at a depth of 80 feet. She wore a 3/8″ full Neoprene II wetsuit, an inflatable buoyancy compensator with tank attached and a webbed belt with 30 lb of free lead weights, used to counteract the positive buoyancy of the wetsuit, that was placed directly on her iliac crests. During the dive she noted a sensation of pressure on her left hip. Upon emerging her left thigh was numb. Six weeks later examination showed sensory loss in the distribution of the left lateral femoral cutaneous nerve. She became asymptomatic over the next four months. Two months later, six months following the initial episode, she again went scuba diving with the same equipment. Immediately thereafter the numbness recurred but subsided in approximately two months. She continues scuba diving but has replaced the original belt that has immovable weights with a shot belt in which the weight is distributed evenly. At present she has no complaints or cutaneous sensory changes.

Our subject, who is 160 cm (63 in) tall, with a 58.5-cm (23-in) waist and a weight of 48.5 kg (107 lb), did not have the abdominal enlargement usually present with meralgia paresthetica. The circumstances leave little doubt that pressure

from lead weights resulted in nerve damage and thigh numbness. No similar cases have been recorded. Scuba diving is a common diversion and occupation. Some of the many participants could be at risk for a compression neuropathy from the above-described mechanism. We propose the term "scuba diver's thigh" as descriptive of this entity and as a means of publicizing an uncomfortable and preventable hazard.

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More on BHT Toxicity

To the Editor: Apropos Dr Grogan's case report of butylated hydroxytoluene (BHT) neurotoxicity,[1] earlier this year we published a case report in *The New England Journal of Medicine* of BHT gastritis.[2] After reading Pearson and Shaw's best-selling book, *The Life Extension Companion*,[3] our patient, who suffered from recurrent genital herpes, ingested 4 grams of BHT on an empty stomach. Within several hours she was experiencing severe epigastric cramping, generalized weakness, nausea and vomiting, and within 48 hours became dehydrated enough to require admission to hospital. Particularly interesting were the concomitant neurologic symptoms of dizziness, confusion and a brief loss of consciousness similar to those noted in Dr Grogan's case report.

Since publication of our letter to the editor, we have had numerous written communications with clinicians both in and outside the United States concerned with the potential toxic effects of BHT in their patients.

Claims of BHT's efficacy for the treatment of herpes simplex in humans are unsubstantiated. Likewise, no well-controlled clinical trials have been done to determine safe dosages in humans despite serious side effects reported in laboratory animals even with comparatively low-dose regimens.[4,5]

The fact that patients waste millions of dollars yearly on ineffective herpes treatments is unfortunate. The fact that some of these "treatments" are potentially toxic is particularly disturbing.

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Treatment for Impotence

To the Editor: Over the past ten years there has been a heightened awareness of the problem of impotence. We appreciated the review of the evaluation of impotence by Dr Cooke in the July issue.[1] However, as an endocrinologist and a clinical psychologist who have seen a large number of patients with impotence, particularly men with diabetes, we would like to offer some suggestions which we have found valuable in our program.

We have found that psychogenic impotence is often very difficult to distinguish from organic causes. Following a complete medical evaluation and appropriate laboratory and hormonal tests, patients should have a psychological assessment by a psychologist or psychiatrist who has a special interest and expertise in diagnosis and treatment of male sexual dysfunctions. We find that a multidisciplinary approach brings us greater success in treating cases of mixed cause. Use of a new ambulatory device called the RigiScan, which allows both the detection of nocturnal tumescence and the simultaneous measurements of rigidity, has helped us in the differential diagnosis of organic versus psychogenic impotence.[2] The documentation of normal erectile function during sleep in impotent men can serve as a biofeedback technique to demonstrate the integrity of their own erectile apparatus.

It should also be pointed out that sexual function may be preserved in mild hypogonadism, may not be corrected with testosterone replacement alone and further diagnostic studies may be needed. Impotence associated with diabetes[3] or antihypertensive drugs may be psychogenic and should not necessarily be ascribed to these organic causes without a comprehensive diagnostic workup. Dr Cooke did not make any mention of the use of the Erectaid,[4] a vacuum device that produces a mechanical erection, nor did she mention the long-term use of intracorporeal papaverine hydrochloride[5] or phentolamine mesylate[6] (or both) in selected patients with erectile failure.

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Unfounded Criticisms of Physicians

To the Editor: As you might expect, Mr Pollock's article "Cut the Cost, Keep the Care" in the August issue[1] riled me more than a little, as it must have many other physicians. To "put doctors on a similar diet" of cost controls infers that we have not already contributed to our share of the challenge of caring for the elderly and the poor. Who is Mr Pollock, or the AARP for that matter, to lump us all together in such a cate-

gory? Am I "in the system" and accept assignment? Does the system pay me on time and fully for my fees? Are my fees reasonable? Do I run an appropriate or excessive hospital census? Do I order unneeded tests? Do I encourage excessive office follow-up? Mr Pollock does not know about me or many other physicians, yet he suggests that we "diet."

To my knowledge the American Association of Retired Persons (AARP) radio spots never mention any ethical approaches to our elderly's problems. Lacking an ethos of order and right and wrong, Mr Pollock and the AARP come through as only another pressure group promoting the self-interests they feel are theirs to demand. We can only hope they will have the stamina to accept the consequences of the system they seek to impose.

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Topics in
Primary Care Medicine

Preventable Complications of Diabetes Mellitus

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

Despite the introduction of insulin therapy more than 50 years ago, the life expectancy of a person with type I diabetes mellitus is about 20 years less than that of a person without diabetes, mainly due to death from cardiovascular and renal disease. Persons with diabetes suffer the complications of loss of limb and sight, and women with type I diabetes are more likely to give birth to infants with congenital anomalies.

Although there is clearly an association between the degree of hyperglycemia and many of these complications, control of blood glucose levels will not be emphasized. Instead, in this article I highlight several other ways that primary care practitioners can help in preventing the complications of diabetes.

Diabetic Eye Disease

Diabetes mellitus is the leading cause of blindness in persons between the ages of 20 and 74 in the United States. A person with diabetes who has retinopathy is almost 30 times likelier to become blind than a person without diabetes. In addition, patients with diabetes are at increased risk of three other types of eye disease: maculopathy, cataracts and glaucoma. Proliferative retinopathy accounts for most of the preventable visual loss in persons with type I diabetes; cataracts, macular edema and glaucoma are mainly responsible in type II diabetes. Effective means of diagnosing and treating all four conditions exist.

Proliferative Retinopathy

Proliferative retinopathy is characterized by the development of new blood vessels in the retina and is usually asymptomatic unless vitreous hemorrhage occurs. Overall, between 3% and 5% of all persons with diabetes have proliferative retinopathy; many more, of course, have background (microaneurysms) or nonproliferative (intraretinal hemorrhages and exudates) retinopathy.

The longer a patient has had diabetes, the greater the risk of proliferative retinopathy. Half of all persons with type I diabetes, and 20% with type II diabetes, have proliferative retinopathy after 20 years of diabetes. In general, persons with type I diabetes who have had their disease for five years or more, and all those with type II diabetes (many of whom have had undiagnosed diabetes for several years) are at risk for proliferative retinopathy. Hypertension is probably an additional risk factor.

Recognizing proliferative retinopathy may be a problem for primary care physicians. In a survey of 193 such physicians in the San Francisco Bay Area, it was found that although 90% examined the optic fundi of their diabetic patients annually, only one of the physicians dilated the pupils. Even through dilated pupils, senior medical residents, internists and diabetologists miss about half of the cases of proliferative retinopathy. Thus, all diabetic persons at risk should be examined by an ophthalmologist; the primary care practitioner should arrange this referral.

Because progression to proliferative retinopathy takes several years, patients without any retinopathy or with background retinopathy only on initial examination can be followed every year or two (perhaps on or about their birthdays, as a convenient reminder). Those who have moderate or severe nonproliferative retinopathy will need more frequent examinations.

Persons with proliferative retinopathy should be treated promptly with panretinal photocoagulation, which has been shown to reduce the incidence of blindness by 50%. It is not known exactly how photocoagulation works; one idea is that it decreases the ischemic stimulus for new vessel formation. The efficacy of tight glycemic control, the use of aspirin,

(Browner WS: Preventable complications of diabetes mellitus. West J Med 1986 Nov; 145:701-703)

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ABBREVIATIONS USED IN TEXT
LDL = low-density lipoprotein
VLDL = very-low-density lipoprotein

aldose reductase inhibitors, photocoagulation of nonproliferative retinopathy and various treatments for vitreous hemorrhage is currently under study.

Maculopathy

Patients with diabetes are also at risk for visual loss due to macular edema, which manifests as thickening of the retina, often with loss of retinal transparency. Unlike proliferative retinopathy, maculopathy is more common in persons with type II diabetes, about 6% of whom have this complication.

Focal photocoagulation has reduced the incidence of further visual loss among persons with maculopathy and decreased vision in trials reported from Great Britain. These results, which were less dramatic than those seen with photocoagulation for proliferative retinopathy, are being evaluated in an ongoing US study.

Cataracts

Persons with diabetes, especially those with long-standing hyperglycemia, are about twice as likely as those without diabetes to have cataracts. More than 20% of diabetic persons have significant visual loss (corrected visual acuity worse than 20/40) associated with cataracts. Surgical treatment, with or without intraocular lens replacement, is about 90% effective at restoring vision. However, many type I diabetic patients with cataracts also have significant retinopathy. Their prognosis is slightly less favorable; in addition, postsurgical complications sueh as retinal detachment may be more frequent.

Glaucoma

Nearly 6 out of 100 patients with diabetes have elevated intraocular pressures. Although there is a type of secondary glaucoma that is unique to diabetes (so-called rubeotic glaucoma, due to neovascularization), the vast majority of diabetic patients with glaucoma have open-angle disease and can be treated with standard therapies. Refractory patients may require laser trabeculoplasty.

Cardiovascular Disease

Persons with diabetes are at increased risk of coronary heart disease, congestive heart failure, peripheral vascular disease and stroke. The usual risk factors—age, hypertension, smoking and hypercholesterolemia—appear to hold. Three of these risk factors are modifiable.

Treatment of hypertension and hypercholesterolemia reduces the incidence of coronary heart disease, stroke and congestive heart failure among persons without diabetes. Because the effects of risk factors are cumulative, the potential benefit of risk factor modification may be even greater in persons with diabetes, especially those with several risk factors. In addition, blood pressure control may be beneficial in preserving renal function and in preventing retinopathy.

Hypertension

About half of all persons with diabetes have high blood pressure (> 140/90 mm of mercury), only 30% to 50% of whom are under control. Diabetic persons with hypertension should be treated with the usual stepped-care approach, beginning with weight reduction and a salt-restricted diet, then adding a diuretic or β-blocker. Serum potassium levels should be monitored: diuretic-induced hypokalemia may worsen glucose tolerance, and severe hyperkalemia can be caused by the potassium-sparing agents (triamterene, amiloride, spironolactone, captopril), especially in patients with type IV renal tubular acidosis. Patients with autonomic neuropathy should receive β-blockers and sympatholytics (methyldopa, clonidine, reserpine, guanethidine) with caution. β-Blockers reduce the adrenergic response to hypoglycemia and may thereby mask its symptoms in patients taking insulin. Impotence may be a problem with many antihypertensive agents; some have suggested that prazosin may be free of this side effect.

Hypercholesterolemia

Diagnosis and treatment of a diabetic patient with hypercholesterolemia is more problematic. Plasma cholesterol is carried in both low-density (LDL) and very-low-density (VLDL) lipoproteins. Only the LDL fraction is known to be atherogenic. Many patients with diabetes, however, have elevated VLDL levels, which causes a mild to moderate increase in total cholesterol. In addition, poor glycemic control can result in elevated cholesterol levels (both LDL and VLDL). This confuses the interpretation of total cholesterol as a risk factor for cardiovascular disease.

All diabetie patients should be advised to follow a prudent (low saturated fat) diet and to exercise regularly. Those who have a substantial elevation of total plasma cholesterol (greater than about 240 mg per dl) on this regimen should have a fasting LDL cholesterol level determined. Treatment with cholestyramine or other bile-acid binders should probably be reserved for patients with serum LDL cholesterol levels greater than about 200 mg per dl despite reasonable glycemic control.

Triglyceride levels need not be routinely measured. An elevated triglyceride level, per se, does not appear to be a cardiovascular risk factor and may just be a result of obesity, poorly controlled hyperglycemia or both.

Smoking

Smoking should be vigorously discouraged. If nicotine-containing chewing gum is prescribed, it should be in conjunction with a smoking cessation program. Although nicotine reduces peripheral blood flow, vascular disease is not a contraindication to the use of nicotine gum; smoking cigarettes has a similar effect.

Amputations

Persons with diabetes are at least 15 times more likely to suffer an amputation than those without diabetes. More than half of all nontraumatic amputations in the US occur in diabetic patients. Among persons with diabetes, about 20% of all admissions to hospital are for foot problems.

Good foot care may reduce the incidence of amputations by more than half. The proportion of physicians, however, who regularly examine the feet of diabetic patients is disappointingly low. In one diabetes clinic, only half of the patients had a foot examination in a given year! On any single visit,

only one in eight patients with diabetes had a foot examination.

The basic tenets of good foot care are outlined in Tables 1 and 2. Physician examination of the feet has the additional benefit of emphasizing the importance of foot care to a patient.

Foot Lesions

The treatment of diabetic foot infections was reviewed in a previous article in this series. Noninfected lesions can be treated conservatively with rest and elevation. Once infection has occurred, debridement and aggressive antibiotic therapy are needed, including anaerobic coverage (such as clindamycin or cefoxitin). Many patients will need hospital care, the exceptions being compliant patients without gangrene or systemic signs who respond to therapy within a few days. Radiographs or a bone scan to rule out osteomyelitis should be done. Nonhealing ulcers associated with ischemia (diminished foot pulses and Doppler pressures) may require angiography and revascularization.

Complications of Pregnancy

Women with type I diabetes have complicated pregnancies and deliveries and are more likely to give birth to infants with congenital anomalies, respiratory distress syndrome, hyperbilirubinemia and hypoglycemia. They should be managed at an obstetrical center that is experienced at treating diabetic pregnancies. Because pregnancy may accelerate the progression of retinopathy in women with type I diabetes, ophthalmologic evaluation is also prudent.

A primary care practitioner is essential in the prevention of unplanned pregnancies and in the preparation for planned ones. A diabetic woman of childbearing age should be taught that organogenesis occurs in the first two months of pregnancy, often before she is aware that she is pregnant or seeks obstetric care. Careful control of blood glucose levels during this critical period can substantially reduce the incidence of serious congenital anomalies. Exactly how tight control should be remains an open question; many authorities recommend attempting to normalize fasting and postprandial blood sugars.

Women in whom gestational diabetes develops are at an increased risk of having infants with macrosomia. Whether or not glycemic control can prevent this problem is unknown.

TABLE 1.—*Good Foot Care: The Physician's Role*

Educate the patient about the importance of foot care and smoking cessation
Examine the feet at each visit. Treat lesions aggressively. Refer problems to an experienced surgeon or podiatrist
Treat risk factors for macrovascular disease
Evaluate the extent of macrovascular disease. Ask about claudication and rest pain. Examine the pulses. Consider noninvasive (Doppler) studies

TABLE 2.—*Good Foot Care: The Patient's Role*

Examine feet daily, using a mirror if necessary. Look for hot spots, cracks, inflammation. If skin is dry, bathe feet in warm (not hot) water, dry thoroughly and rub in lanolin or mink oil
Do not smoke
Change shoes twice a day. Wear shoes with leather uppers, which mold to the feet. Be especially careful when wearing new shoes
Cut toenails straight across
Never walk barefooted
Take off your shoes and socks each time you visit the doctor

Conclusions

The primary care practitioner has an essential role in preventing many of the complications of diabetes mellitus. Concern over achieving satisfactory control of blood glucose concentrations should not diminish efforts to ensure that diabetic patients receive regular ophthalmologic examinations, good foot care and have their cardiovascular risk factors controlled. Diabetic women of child-bearing age should be counseled about the importance of planned pregnancies and advised to obtain early prenatal care when pregnancy occurs.

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Seminars in Health Care Delivery

Changing Physician Payment for Medicare Patients

Projected Effects on the Quality of Care

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This feature will appear regularly in The Western Journal of Medicine. *It is intended to cover recent developments in a broad range of issues that will have an impact—either directly or indirectly—on clinical practice. Occasionally the seminars may include informed speculation about likely future developments.*

STEVEN A. SCHROEDER, MD
Series' Editor

Congress and the Reagan Administration, in an effort to "contain" costs, are considering changes in the way physicians are paid when they care for Medicare patients. By examining the effects on quality of care of several alternative ways physicians might be paid, including modified fee for service, physician diagnosis-related groups and capitation through health maintenance organizations, we can predict the kinds of effects on quality of care most likely to occur and the kinds of patients most likely to be affected. Under each of the payment alternatives, poorer and sicker patients are at greatest risk for reduced access to care and quality of care. These findings underline the need for rigorous experiments to assess the effects of changes in physician payment on quality of care and the need for monitoring and assurance of quality in a new payment system.

(Hammons GT, Brook RH, Newhouse JP: Changing physician payment for Medicare patients—Projected effects on the quality of care. West J Med 1986 Nov; 145:704-709)

Congress and the Reagan Administration are considering changes in the way physicians are paid when they care for Medicare patients. Insurance companies have begun to modify reimbursement methods for physicians' services. The driving force behind these changes is the perceived need to "contain" costs. In addition, the fee-for-service system used by Medicare to reimburse physicians has been criticized because it rewards technical services (doing a biopsy) more than cognitive ones (talking to a patient).

Alternative methods to pay for physicians' services have been proposed. Each is being evaluated primarily for its potential to slow increases in costs of medical care. Effects on access to care and quality of care, however, are also being considered. We have recently attempted to project (the data to do more than project are absent) the effects of alternative payment methods on the quality of care delivered to Medicare beneficiaries.[1] In this paper, we will briefly describe these alternative payment methods and summarize the likely effects of each on the quality of care. We are unable to predict the precise impact with any confidence. We are able to suggest the kinds of effects that are most likely to occur and the kinds of patients who are most likely to be affected.

The uncertain impact implies a need for rigorous, experimental assessment of changes in payment mechanism on quality of care and for monitoring and assurance of quality of care in any new payment system. By predicting the possible

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ABBREVIATIONS USED IN TEXT
DRG = diagnosis-related group
HMO = health maintenance organization

effects of a change, the work reported here can guide the design of activities to assure quality of care if an alternative payment system is adopted.

Alternatives to the Current Physician Payment System

The traditional basis for Medicare's reimbursement of physician services has been "customary, prevailing and reasonable charges" for each of many units of service.[2-4] Recent modifications to increase the incentive to accept assignment do not affect many traditional criticisms of the current reimbursement system—namely, that it is inflationary; lacks an incentive to provide medical services efficiently, and inappropriately encourages the provision of inpatient care, surgical services and technical procedures over outpatient, medical and more "cognitive" services.[3,5-8]

Alternative payment methods differ from the current Medicare fee-for-service system in several ways: the relative remuneration for different physician services, the unit of services for which a physician is paid (such as an entire hospital stay instead of each patient visit) and organizational influences such as the freedom with which a physician can order a service.[3,5,9,10] We will briefly describe three possible methods. A more extensive discussion of alternative physician payment methods can be found in Jencks and Dobson[5] or a recent report from the Office of Technology Assessment.[10]

Fee for Service With Revised Fee Schedule

Under one alternative, physician services would be reimbursed by fee for service according to an explicit fee schedule, with both relative and absolute fees for each service determined by some means other than the customary, prevailing and reasonable mechanism. Such a fee schedule might be based on studies that impute a cost for providing each of several types of physician visits and procedures as illustrated by the approach of Hsiao and Stason,[11] or in other ways.[5]

We will not specify how the fee schedule is determined, but will assume that the resulting fee schedule differs from the customary, prevailing and reasonable fees now used as follows: it reduces (for similar services, such as a routine office visit) differences between fees that Medicare would pay specialists and generalists; it reduces the difference Medicare would pay for similar services when done in an inpatient versus an outpatient setting, and it reduces the difference in net physician compensation per hour paid by Medicare for surgical and technical procedures relative to medical and more cognitive services.

Physician Diagnosis-Related Groups

Under payment by physician diagnosis-related groups (DRGs) for inpatient physician services, a single payment would be made for all physician services associated with an admission to hospital, including fees of consultants; the payment would not include hospital costs or ancillary services now covered by the hospital payment under Medicare's prospective-payment system. Payment for each patient would be adjusted by the same disease categories (DRGs) now used for Medicare hospital payment.

The recipient of the lump sum payment could be the attending physician, who would contract with consulting physicians for their services and pay them out of the lump sum. Alternatively, the lump sum could be paid to the hospital staff, with subsequent distribution of the payment among individual physicians according to rules established by the hospital staff—for example, each physician could be paid a share based on accumulated units of work. Other possible arrangements, such as payment of the lump sum to the hospital,[5] will not be considered here.

Health Maintenance Organizations for Medicare Beneficiaries

The increased use of capitation payments for Medicare beneficiaries has received much attention.[5,10,12] One version of this option is to expand the use of health maintenance organizations (HMOs) and similar prepaid plans by Medicare beneficiaries; HMOs that enrolled Medicare beneficiaries would conform to rules established by Medicare. Medicare has already begun to increase the use of HMOs by Medicare recipients.[13] Few Medicare beneficiaries are now enrolled in HMOs. We will consider the effects on quality of care of large increases in the number of Medicare beneficiaries in HMOs.

The Influence of Physician Payment Mechanisms on Quality of Care

The quality of personal medical care can be considered to be composed of the quality of technical care, the quality of the art of care and the interaction between the two. Quality of technical care includes the adequacy of the diagnostic and therapeutic processes. The art of care relates to the manner and behavior of the provider in delivering care to and communicating with a patient.[14] High quality of care should be reflected in good patient outcomes, such as emotional well-being, adequate physical capacities for carrying out ordinary tasks or at least a reduction in the rate of decline in health status.[15]

The quality of personal medical care is in large part determined by the amount and type of medical services used, including physicians' time and effort, and the way these services are used to diagnose and treat a patient's condition.[1] In an ideal world, decisions about which services to use would be made jointly by physician and patient in an effort to improve the patient's health as the patient perceives it; these decisions include which diagnostic services to use, whether to prescribe drugs and whether hospital care is needed. Each physician payment mechanism can be examined in an attempt to predict how it will change these patient care decisions and, in turn, how quality of care would be affected.[1,16]

Physician payment systems contain different financial incentives that could influence both patient and physician decisions. The financial incentives facing patients affect their decisions through out-of-pocket costs. If one patient's out-of-pocket costs from deductibles and coinsurance are greater than another's, that patient will on average receive less care.

The physician's ethic requires that physicians function entirely as patients' agents, considering only the patients'

interests when making patient care decisions; physicians are not to consider their own financial or other interests. It is reasonable to assume that physicians sometimes fall short of this ideal. If a physician is considering doing a nonrisky diagnostic procedure that has only a small chance of contributing useful information, he or she may be more likely to do the procedure if a large fee is involved. A surgeon may be less likely to ask a consultant to see a patient before a surgical procedure if the consultant's fee must be paid out of the fixed sum that the surgeon receives for the operation. In marginal or "grey" areas, financial considerations will affect some patient care decisions. This in turn can influence quality of care.

Alternative payment systems may also entail major changes in the organization of medical care. For instance, the care provided through an HMO differs from that in fee for service not only in the financial incentives facing physicians and patients, but also in the organizational structure in which care is provided. An HMO may require more utilization review or may require practice in a multispecialty environment. The HMO may restrict the availability of hospital beds or consultations.[1,16]

It is difficult to predict with confidence the precise effects on quality of care of alternative physician payment mechanisms.[1,16] The task is made more difficult by the presence of extensive changes in medical care in the United States in the past few years, such as the increasing supply of physicians and the institution of Medicare's prospective-payment system. Much uncertainty remains as to the effects of each alternative system. We assert that this uncertainty calls for experiments to test rigorously the effects of alternative physician payment systems on quality of care, and for new efforts to monitor and assure quality.

Effects on Quality

Fee for Service With Revised Fee Schedule

The prevailing fees that Medicare now pays are generally higher for similar services rendered in hospital than in an ambulatory setting, for more technical services and surgical procedures than for less technical services and for similar services provided by more specialized than by less specialized physicians. We assume that a new fee schedule would narrow these differences. The amount that Medicare would pay would increase relatively for outpatient services, for less technical services such as patient counseling and for services from less specialized physicians. Physicians would receive relatively more from Medicare for these services than under the present system. This would result in an increased financial incentive to provide these services. Amounts payable by Medicare would decrease relatively for most inpatient services, for technical services such as endoscopy or surgical intervention and for services from specialists. Physicians would receive less from Medicare for these services than they do now.

The changes in the amounts Medicare would pay would affect patients' out-of-pocket costs for services from physicians who do not accept assignment. If physicians did not change their charges in response to the changes in the amounts Medicare would pay, patients' out-of-pocket costs would increase (compared with the present payment system) for inpatient services, surgical and technical services and specialist services. Out-of-pocket costs would decrease for outpatient and nontechnical services and services from less specialized physicians. These changes in out-of-pocket costs would provide incentives for patients to purchase fewer inpatient and technical services and services from specialists and more outpatient and nontechnical services. In addition, over time, physicians would be expected to alter their charges toward the amounts specified in the new Medicare fee schedule.

Competition among physicians would tend to result in lower fees charged by specialists and lower charges for inpatient, technical and surgical services. This, in turn, would reduce out-of-pocket costs to patients. We would not expect physicians' charges to fall to the Medicare reimbursement rate, however, especially if other payers did not adopt Medicare's fee schedule. If the resulting out-of-pocket costs remained too high, there could be political pressure to limit them by, for instance, requiring physicians to accept assignment for Medicare reimbursement. Physicians might respond to reduced fees by attempting to increase the number of services provided, but this would be limited, at least for hospital services, by utilization review of those services monitored by organizations such as peer review organizations.

In sum, compared with the present payment system, patients would tend to face higher out-of-pocket costs for and to reduce their purchases of inpatient and technical and surgical services; to face lower (or zero) out-of-pocket costs, and to increase their demand for comparable outpatient services, less technical services and services from less specialized physicians. Physicians would have an increased financial incentive to provide outpatient services and less technical services than they do now.

The impact of these changes on quality of care depends on assumptions made about the response of patients to changes in the price of physicians' services and the response of physicians to changes in their incomes. These assumptions are developed more fully elsewhere.[1] Compared with patterns of care under the present physician payment system, we predict the following would occur:

- Patients would use more outpatient services, and services of all kinds would tend to shift to the outpatient setting; patients would tend to be admitted to hospital less frequently.
- Patients would tend to use fewer surgical and technical procedures and to increase their use of less technical or "cognitive" services such as physician visits and counseling time. The mix of services provided by most physicians would also shift in these directions.

These changes would be more likely to occur among poorer patients because out-of-pocket costs would have a more powerful influence on their choices; for example, when compared with the present situation, poorer patients would be less likely to be cared for by specialists or to receive technical procedures than well-to-do patients. This conjecture is supported by results from the Rand Health Insurance Experiment.[17,18]

What are the expected differences in the quality of the care received under the "new" fee schedule? The answer depends in part on what one believes about the patterns of care in the present system. If one believes that there are now excessive or unnecessary admissions to hospital, surgical and diagnostic procedures, laboratory tests and the use of specialists, then reduction in these services or substitution for them by services

such as additional physician time or services from less specialized physicians may lead to improvements in the quality of care on average (though in any particular case there may be a shortfall).

There is some evidence that before Medicare's prospective-payment system was instituted, there were unnecessary admissions and days of hospital care, unnecessary operations and unnecessary laboratory tests for Medicare patients in hospital.[1] However, the decrease in hospital admissions and days of care for Medicare patients since the institution of the prospective-payment system[19] may make the excess use of these services now less likely. Whether reducing the use of specialists would diminish the quality of care is uncertain.[1]

Thus, it is difficult to predict the overall effects on quality of care of the changes in the use of services expected under such a revised fee schedule. For some patients the quality of care would likely improve due to the change in mix of services received, and for others it would decline. Some patients would benefit from increased physician time and counseling; a patient with hypertension may achieve better blood pressure control and have a reduced risk of stroke. Perhaps some patients would benefit from forgoing a surgical or technical procedure with little expected benefit. For these patients, quality of care would improve. Some patients, however, would postpone or fail to receive a beneficial operation or an expensive procedure, or choose to forgo needed services from specialists.

Most of the changes in quality of care likely to occur would be small; most would occur in the "grey areas" of medical decision-making. Poorer people and others for whom out-of-pocket costs are more important, particularly those with chronic or complex illness who require many technical medical services or more specialized or expensive services, would be more likely to forgo needed medical services. They would be expected to represent a disproportionately large fraction of persons receiving lower quality of care under the new revised payment system. Poorer persons, however, would also be more likely to benefit from reduced out-of-pocket costs for outpatient services and less technical services.

Physician DRGs for Inpatient Physician Services

The effects of paying a prospectively determined lump sum for all physician services associated with an episode of inpatient care depend on how the payment system is designed.[1,5] Who receives the payment and how it is distributed among the physicians participating in the care of the patient are particularly important. We will consider two cases. In both cases, assignment will be considered mandatory.

In the first, the attending physician (perhaps the admitting physician) receives the payment and as the gatekeeper physician "hires" other physicians who also provide care to the patient. The administrative burden on the attending physician would be substantial. In the second, the lump sum payment is made to the medical staff of the hospital, and the payment is distributed among those physicians caring for the patient according to the weighted fraction of charges submitted by each physician. If total charges were to exceed total payment, then each physician would receive less than a dollar for each dollar he or she charged.

Attending physician model. If the attending physician receives the physician DRG payment, the risks of significant financial gains or losses are substantial.[20] There are several possibilities for reducing this financial risk, including the liberal use of outlier payments[1]; we assume that some means of reducing the risk to the attending physician will be used, though a financial risk to the attending physician is still present.

Attending physicians have a financial incentive to reduce expenditures for consultations or procedures that they believe are of minimal benefit to the patients they admit. This could increase the efficiency and reduce the cost of inpatient care. As noted earlier, the available evidence suggested that before the beginning of Medicare's prospective-payment system, some unnecessary inpatient services were provided under fee-for-service reimbursement of physicians and cost-based reimbursement of hospitals. Lengths of stay have already been reduced under prospective payment. It is not clear whether additional reductions in inpatient services can be made without disproportionately reducing the quality of care.

The incentives facing attending physicians may also lead to skimping on their services to patients or on needed consultant physician services, particularly for patients whose costs of services are in excess of a physician DRG payment. Such patients may fail to receive needed services of specialists or may be discharged prematurely, with an increased risk of mortality and morbidity and reduced quality of care. There is a potential for disruption of and damage to relationships among physicians and of medical consultation practices,[21] with adverse effects on the quality of both inpatient and outpatient care.

Patients who are likely to require resources costing much more than an expected physician DRG payment may have difficulty finding a physician willing to admit them to hospital or to assume responsibility for their care: they will suffer reduced access to care. If both physician and hospital are paid on a DRG basis, the incentive for both to avoid caring for or to "dump" such patients may be very strong.

Under the current prospective-payment system for hospitals, patient care including surgical procedures has been shifted to the outpatient setting. This has not necessarily reduced the volume of procedures or the incomes of physicians. Under physician DRGs, there would be an additional incentive to shift care of patients to the less-regulated outpatient setting, particularly for those patients for whom the expected physician DRG payment for inpatient care is considered inadequate. If care is inappropriately shifted, the risk to patients is increased.

In sum, physician DRGs paid to attending physicians provide incentives to increase the efficiency of inpatient care in addition to those embodied in the hospital prospective-payment system. This system of physician payment, however, also poses considerable risks of skimping on inpatient care and reduced access to care, particularly for those patients likely to require services costing more than the physician DRG payment.

Hospital staff. Payment of the physician DRG sum to the hospital staff allows pooling of financial risks across a number of physicians and a larger number of patients. Lowering each individual physician's risk of financial loss would be expected to reduce the risk of skimping on needed physician services for patients admitted to hospital and may mitigate the threat of

reduced access to inpatient care for potentially "unprofitable" patients. If the medical staff is well organized, however (and particularly if it cooperates closely with the hospital), the threat to access for those patients may be substantial.

Physicians whose practices consist largely of patients likely to require more services than average for the physician DRG, such as the more severely ill patients within each DRG, may be perceived to be sources of financial losses by the rest of the medical staff. There may be pressure on such physicians to alter their patient mix or even—if the hospital beds can be filled by patients from other physicians—efforts to remove them from the hospital staff.

In summary, the risks of reduced access to care and reduced quality of care are present under both kinds of physician DRGs, though these dangers may be smaller with payment to the medical staff than with payment to the attending physician. These risks could be reduced by adherence of physicians to the medical ethic, by effective utilization review and quality assurance by peer review organizations, by the risk of malpractice litigation and perhaps by competition from other physicians for patients.

Increased Enrollment of Medicare Beneficiaries in HMOs

HMOs provide medical care to their enrollees at lower cost than fee-for-service medicine, largely through lower use of hospital care.[22] HMOs have a financial incentive to control the use of services by their enrollees, including services that are of little or no benefit. This incentive may be passed on to physicians in an HMO directly, or may be translated into utilization controls imposed on physicians.[23,24] This incentive could also lead to underprovision of needed services and reduced quality of care.

HMOs also have an incentive to avoid enrolling persons who are likely to use large amounts of services unless the capitation payment is accurately adjusted for this increased expected cost. Without such a careful adjustment or the adoption of some mechanism to prevent adverse selection of enrollees by HMOs, access to care may be reduced for those persons with chronic illnesses or who otherwise require extensive medical services.

Physicians in HMOs operate under more organizational controls than do fee-for-service providers.[8,23,25] If there is increased internal review by group physicians, the quality of care might be improved. If physicians were not allowed to order needed specialist consultations, quality of care could suffer. The effects depend critically on the ways HMOs influence their physicians.

Review of assessments of care provided by HMOs leads to the conclusion that established prepaid group practices can provide care to their enrollees of technical quality comparable to that provided in fee-for-service medicine and can provide this care at a lower cost; consumer satisfaction, however, is lower in HMOs.[1,8,21,23,25–28] It is unwarranted, however, to conclude that extending HMO care to a much larger fraction of the population, and particularly to the elderly under Medicare or the poor, would not threaten quality of care for these groups. There is simply little experience with provision of care by HMOs to the elderly or poor: most HMO enrollees are young and employed. Compared with the population usually served by HMOs, the poor and the elderly will more often need continuity of care for management of chronic conditions, and may more frequently need specialized care for complicated conditions. Physical barriers and bureaucratic complexities of an HMO that are easily managed by an employed population may be difficult impediments for elderly enrollees. On the other hand, lower out-of-pocket costs in HMOs may result in greater financial access to services for poorer Medicare enrollees. Finally, newer organizations operating as HMOs may differ in important respects from traditional prepaid group practices. If newer HMOs are organized to increase the individual financial risk to primary physicians for the costs of their referrals or other services used by patients assigned to them (the gatekeeper model), then the possibility of skimping on needed care would increase.

For traditional HMOs to provide care to the elderly or poor of quality equivalent to the care provided to their current enrollees, they may have to modify their medical and administrative practices in response to the special needs of elderly and chronically ill persons. If growth in enrollment is rapid in established HMOs, or if new HMOs are less well run than the established HMOs, quality of care may suffer.

In sum, the increased use of HMOs offers the possibility of maintaining the quality of medical care while controlling costs, but there is much uncertainty. The need for monitoring the quality of care as more people receive care through HMOs is clear. An evaluation now under way of several demonstration projects with Medicare beneficiaries in HMOs includes assessing quality of care.[29] Such efforts will become even more important if the number of Medicare beneficiaries and the poor enrolled in HMOs is to be rapidly increased.

Summary and Conclusions

It has proved difficult to predict the effects on quality of care of changing the way physicians are paid for their services. Each of the alternatives considered here holds out the possibility of either increasing or decreasing the quality of care. It is not possible to determine which result will occur. We can predict that the effects on quality of care will not be uniform: some groups of patients are likely to benefit and some to suffer. Under each of the alternatives, those Medicare beneficiaries who are poor or who suffer complex chronic illnesses appear to be at greatest risk of reduced access to care and reduced quality of care.

The uncertainty about the effects of each proposed change suggests a need for several steps to prevent or minimize the untoward effects of a new payment system on quality of care. First, an experiment to test the impact of a proposed change would allow assessment of its effects on access to care and quality of care—as well as cost of care. Such an assessment would require collecting data on the outcomes and processes of care.[1,30] If adverse effects such as premature mortality, decreased functioning and quality of life or increased morbidity were found to occur, the new payment system could be altered before it did widespread harm. Second, to prevent short-term harmful effects from occurring if a change in physician reimbursement is implemented nonexperimentally, the quality of care should be carefully monitored and appropriate "real time" responses made to minimize the adverse effects on patient care. The kinds of effects most likely to occur can be predicted by analyses such as those reported here. These predictions can serve as guidelines for focusing efforts to prevent deterioration in quality of care.

Extensive changes in our system of providing medical care and of its financing appear to be inevitable. The challenge to the medical community is to prevent these changes from adversely affecting quality, especially for society's more vulnerable—the poor and the sick.

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Quality of Care for Psychotropic Drug Use in Internal Medicine Group Practices

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To evaluate the care given by internists in group practices at 16 academic medical centers to patients who used minor tranquilizers or antidepressants, data were abstracted from medical records and compared with specific criteria for quality care.

Of 1,532 continuing care patients, 18% used minor tranquilizers and 7% used antidepressants. Almost 90% of antidepressants were prescribed for depression and 50% of minor tranquilizers were prescribed for mental health problems. The group practice internists performed well on concrete aspects of care, such as avoiding giving minor tranquilizers intravenously or intramuscularly and scheduling follow-up visits. Relatively few patients, however, had an adequate treatment plan noted in the chart. About 25% of users of minor tranquilizers did not have an acceptable indication for the drug noted in the chart. Less than 10% of users of minor tranquilizers had a plan for discontinuing the drug use; yet, 35% had long-term regular use.

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Most prescriptions for psychotropic drugs in the United States are written by nonpsychiatrist physicians.[1,2] We know very little, however, about the quality of the practices of these physicians in prescribing psychotropic drugs. Are these drugs prescribed for appropriate clinical indications? Are goals for treatment identified? Do follow-up visits occur? In this paper, we answer these questions for internists in group practices in academic medical centers. We describe their care in prescribing or monitoring the use of minor tranquilizers and antidepressants.

Recent research findings and policy trends support the importance of answering the questions posed above. Primary care physicians are now known to deliver mental health care to a substantial proportion of patients; that care typically includes psychotropic medication.[3-6] Several prepaid health programs have recently implemented or proposed a "gatekeeper" policy in which patients are reimbursed for services from mental health specialists only on referral by a primary care physician. Under gatekeeper policies, primary care physicians may assume increased responsibility for prescribing psychotropic drugs.

In the past, studies have been done of a variety of patient groups (such as users of drugs in the general population, patients in medical or psychiatric outpatient clinics) and methods (patient surveys, physician surveys, medical chart audits) to evaluate prescribing practices of nonpsychiatrist physicians.[7-12] Conclusions from these studies have varied. For example, some studies found that psychotropic drugs were often prescribed for appropriate physical or psychiatric symptoms.[1,9,11,12] Other studies found that nonpsychiatrist physicians were likely to select inappropriate psychotropic medications—that is, an antianxiety agent to treat depression—or to prescribe some drugs, such as antidepressants, in subclinical dosages.[7-9]

Although numerous studies describe aspects of primary care physicians' practices in prescribing psychotropic drugs, very few have compared these practices with preestablished standards—the hallmark of quality-of-care studies.[13] Existing studies focus on inpatient psychiatric care[14-18] or practices in prescribing neuroleptics.[19] The American Psychiatric Association has developed standards for peer review of psychotropic drug use that have been endorsed by the American

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ABBREVIATIONS USED IN TEXT
BIAC = Beth Israel Ambulatory Center
RWJF = Robert Wood Johnson Foundation

College of Physicians and the American Academy of Family Physicians.[20] While the criteria and their endorsement by nonpsychiatrist physicians represent a significant advance in the development of quality-of-care criteria, empirical comparisons of care delivered with the criteria have not been published.

Methods

Patients and Design

We studied all 15 practices participating in the Teaching Hospital General Medicine Group Practice Program funded by the Robert Wood Johnson Foundation (RWJF)—see the study published by Kosecoff and co-workers.[21] The RWJF provided each practice with a four-year, $800,000 grant to provide continuous, personalized general medical care to adult patients. The programs were modeled on the Beth Israel Ambulatory Center (BIAC) in Boston, which we also studied.

The participating practices were located at Albany Medical College of Union University (Albany, NY), University of Colorado Health Sciences Center (Denver), Georgetown University Hospital (Washington, DC), Johns Hopkins Hospital (Baltimore), University of California at Los Angeles, Mount Sinai School of Medicine of the City University of New York, New England Memorial Hospital (Boston), University of Medicine and Dentistry of New Jersey (Piscataway, NJ), North Carolina Memorial Hospital (Chapel Hill, NC), University of California at San Francisco, Saint Louis University Medical Center (St Louis), Vanderbilt University Medical Center (Nashville, Tenn), West Virginia University Medical Center (Morgantown, W Va), Medical College of Virginia (Richmond, Va) and the Yale-New Haven Hospital (New Haven, Conn).

In each practice, a random sample of 100 continuing patients was identified from the appointment log. A continuing patient was defined as any patient whose first visit to the practice occurred at least six months before the index visit. Data were abstracted from the complete medical record of all patients who agreed to participate.

Quality of Care

We developed criteria for quality care in treating patients with minor tranquilizers—that is, antianxiety agents and sleeping pills—and antidepressants (Table 1). The criteria were based on the American Psychiatric Association's criteria for peer review of psychotropic drug use and other drug use review programs.[20,22-24] The criteria were modified after reviews provided by each group practice. Given the difficulty of determining appropriate indications for drug use from the medical record, criterion 1 (indications) was purposely specified very broadly (for instance, a diagnosis of any neuroses as an indication for minor tranquilizers). Disorders thought to be exacerbated by stress, however, such as hypertension, were not considered acceptable indications unless a coexisting emotional problem was also noted.

Our criteria focus on physicians' management strategy—that is, goals of treatment—rather than on the appropriateness of the specific drug or dosages prescribed. We assumed that these physicians have responsibility for monitoring the use of psychotropic drugs prescribed by out-of-practice physicians.

At each institution, a trained evaluation coordinator abstracted data from the medical record of each patient who, during the abstraction period, was either already using a sedative/hypnotic or an antidepressant or who received a new prescription. Diagnoses and symptoms were recorded according to the terminology used by the providers (such as neurosis). The abstraction period included the entire period that a person had been enrolled in the group practice.

Characteristics of Patients

The medical record abstraction included data on demographic characteristics of patients and the use of services in the practice and other locations in the practice institution.

Statistical Analyses

We determined the extent to which all RWJF group practices met each quality-of-care criterion. We determined the mean and range across practices of meeting each criterion. We separately described the performance of BIAC, the practice after which the others were modeled.

Results

Characteristics of Continuing Patients

Of the continuing patients enrolled in the study, complete data were obtained from the medical records of 1,532 (98%). Table 2 presents descriptive characteristics on the sample for the 15 RWJF group practices combined and for BIAC. While age and sex distributions are similar for all practices, patient ethnic mix and sources of payment vary significantly by prac-

TABLE 1.—*Quality-of-Care Criteria*

Anxiolytics and Hypnotics

Criterion 1 (indications). If a sedative/hypnotic was prescribed on an outpatient basis, then the patient carried 1 of the following diagnoses: neurosis, anxiety disorder, alcoholism, musculoskeletal disorder of the neck or spine or sleep disorder.

Criterion 2 (no long-term use). The patient was not a regular user of a sedative/hypnotic for more than two consecutive months, unless there is a stated reason for continued use. "Regular" use is defined as once a day or more.

Criterion 3 (no outpatient injections). The patient did not receive an outpatient injection of a sedative/hypnotic.

Criterion 4 (follow-up plans). If the patient received an initial prescription for a sedative hypnotic, then a follow-up visit was scheduled.

Criterion 5 (treatment plan). The patient using a sedative/hypnotic has a treatment plan documented in the chart, defined as a plan for other therapy for the problem such as counseling by the practice provider or a psychiatrist; or both the goal of drug therapy is stated and the criteria for discontinuing the drug are noted in the chart.

Antidepressants

Criterion 1 (indications). If an antidepressant was prescribed, there is a diagnosis of depressive or affective disorder, signs or symptoms (or both) of depression, chronic pain disorder, headache or migraine noted in the chart.

Criterion 2 (treatment plan). The patient using an antidepressant has a treatment plan documented in the chart, defined as a plan for other therapy for the problem or both the goal of drug therapy and the criteria for discontinuing the drug are noted in the chart.

Criterion 3 (follow-up plans). If an antidepressant was prescribed, then a follow-up visit was scheduled.

Criterion 4 (follow-up occurred). If an antidepressant was prescribed for the first time, then a follow-up visit or telephone call occurred within 6 weeks.

tice setting. Before enrolling, patients received care in the practice settings for periods ranging from 1 to 2 years, with a mean of 14 months for the RWJF group practices.

Across practices, about 40% of patients received their care primarily from a faculty member and a similar percentage from house staff (Table 2). BIAC relies significantly more on nonphysician providers than the RWJF practices. The percent of patients who primarily visited a member of the house staff ranged from 9% to 63%, depending on the practice.

All practices treat a wide range of diagnoses. The six most common diagnosis clusters are hypertension (60% of patients); nonspecific symptoms (40%); depression, anxiety or neuroses (30%); obesity (25%); degenerative joint disease (25%), and diabetes mellitus (22%).

Use of Psychotropic Drugs

Of continuing patients in the RWJF practices, 18% used a minor tranquilizer and 7% used an antidepressant during the study period (Table 3). Virtually all of the antidepressants prescribed were tricyclic antidepressants. Across all practices, male and female patients do not differ significantly or appreciably in the prevalence of use of either minor tranquilizers or antidepressants. The mean age of users of sedative hypnotics is 57 years; the mean age of users of antidepressants is 55 years. By comparison, the mean age for all continuing patients is 55 years (Table 2).

For RWJF patients, the average number of months of use is nine for sedative/hypnotics and seven for antidepressants (Table 3). BIAC prescribes minor tranquilizers to a significantly higher percentage of patients than the RWJF practices. Further, when antidepressants are prescribed, they are continued for a longer period of time (Table 3).

Quality of Care—Minor Tranquilizers

As shown in Table 4, a diagnosis of neurosis, anxiety or alcoholism (the acceptable mental health indications) is listed in the charts of 54% of users of minor tranquilizers in the 15 RWJF practices. When physical health reasons are included, about 75% of all users have an acceptable indication noted (criterion 1). In some practices, about 50% of patients did not have an acceptable indication for drug use noted (Table 4). Across practices, the most common indications for the use of minor tranquilizers are neurosis, sleep disorder, anxiety and musculoskeletal disorder of the neck or back.

Criterion 2 evaluates the extent to which practices avoid long-term use of minor tranquilizers. As shown in Table 4, about 35% of users of minor tranquilizers had daily use for more than two months. Most of the practices with a high proportion of long-term users also provide some reasons for that level of use. As a result, the RWJF practices meet the complete criterion for 90% of users.

All of the practices performed well on criterion 3. Only four practices have any patients who received outpatient injections of minor tranquilizers.

Across the RWJF practices, 86% of patients who received their initial prescription for a minor tranquilizer during the study period had a scheduled follow-up visit (criterion 4—see Table 4). Almost all patients who were not scheduled for a follow-up visit were asked to return "PRN" (as needed).

The practices fulfill the treatment plan criterion (criterion 5) for only 30% of patients (Table 4). The percentage of

TABLE 2.—*Characteristics of Continuing Treatment*

Patient Characteristic	*BIAC*	*RWJF Group Practices*
Number of patients	100	1,432
Mean age, years	53	55
Sex female, %	70	69
Race white, %	46	45
Has Medicaid or Medicare, %	50	53
Mean duration of care in the group practice, mo	17	14
Regular provider (percent of patients)		
Faculty physician	36	43
House staff	41	46
Nonphysician	22*	10

BIAC = Beth Israel Ambulatory Care Center, RWJF = [funded by the] Robert Wood Johnson Foundation

*Significantly different from RWJF practices, $P<.05$.

TABLE 3.—*Psychotropic Drug Use During Study*

Type of Use	*RWJF Group Practices N = 1,432*	*BIAC N = 100*
Minor tranquilizer		
Patients with any use, %	18	34*
Mean duration of use per user, mo	9	10
Antidepressants		
Patients with any use, %	7	4
Mean duration of use per user, mo	7	14

BIAC = Beth Israel Ambulatory Care Center, RWJF = [funded by the] Robert Wood Johnson Foundation

*Significantly different from RWJF practices, $P<.05$.

TABLE 4.—*Minor Tranquilizers—Quality-of-Care Criteria*

Abbreviated Criterion	*Users Meeting the Criterion, Percent**		
	BIAC	*RWJF Group Practices*	
		Combined	*Range Across Practices*
Criterion 1 (indications)			
Acceptable mental health reasons	35†	54	17-85
or physical health reasons‡	73	76	47-100
Criterion 2 (long-term use)			
No long-term use	68	63	0-88
or documentation of long-term use‡	74†	90	73-100
Criterion 3 (injections)			
No outpatient injections	100	98	87-100
Criterion 4 (follow-up)§			
Visit scheduled‡	30†	86	55-100
or return as needed	30†	94	67-100
Criterion 5 (treatment plan)			
1. Counseling	21	28	0-100
2. Purpose stated	24†	46	0-90
3. Plan for stopping	12	6	0-19
Either 1 or (2 & 3)‡	29	31	0-100

*RWJF (funded by the Robert Wood Johnson Foundation) practices have 259 users, BIAC (Beth Israel Ambulatory Care Center) has 34 users.

†Significantly different from the average of the 15 RWJF group practices combined, $P<.05$.

‡The formal criterion.

§New prescription only.

patients meeting this criterion varies significantly by practice—from 0% to 4% to as high as 75% to 100%. Practices with high percentages of patients meeting the criterion do so by offering concurrent counseling. Very few patients in any of the practices have any notation of criteria for discontinuing drug therapy—despite the relatively high number of users with long-term use.

Quality of Care—Antidepressants

As shown in Table 5, for the combined RWJF group practices, 98% of users of antidepressants have an acceptable indication for drug use noted in the chart (criterion 1). Most users are prescribed antidepressants for a diagnosis or signs or symptoms (or both) of depression. Across the RWJF practices, 60% of users of antidepressants have two or more signs or symptoms (or both) of depression (excluding the diagnosis) noted in the chart.

About half of users have a documented treatment plan for antidepressants; there is considerable variation among practices in meeting this criterion (Table 5). Across all practices, 50% of users of antidepressants are offered concurrent counseling. For the RWJF practices, nearly half of users have a stated goal for treatment. Relatively few patients have any plan for discontinuing the medication noted in the chart (Table 5).

Criteria 3 and 4 evaluate follow-up plans for patients receiving their initial prescription for an antidepressant during the abstraction period. Of all such patients in RWJF practices, 88% had a visit scheduled. Most patients actually had a return visit within six weeks of the initial prescription of antidepressants (Table 5).

Discussion

Efforts to understand the practices of primary care physicians in providing mental health care to their medical patients have greatly increased in recent years.[3-6,25] The findings of the current study support the importance of these efforts. A third of all continuing care patients seen in academic internal medicine group practices had a diagnosis of anxiety, depression or alcoholism. Nearly 20% of patients were prescribed a minor tranquilizer and half of these received the drug for a mental health problem. About 7% of patients received an antidepressant—most for treatment of depression. The high rate of psychotropic drug use is consistent with previous studies of outpatient medical settings.[1,7,8,11] By comparison, the prevalence of the use of minor tranquilizers in general population samples in the United States during the 1970s was estimated at between 9% and 15%.[6-29]

The principal focus of our study was on determining the quality of care for patients taking minor tranquilizers and antidepressants. In the absence of previous empirical studies of specific criteria, we developed criteria for several components of care that we thought were clinically important and appropriate for the chosen method (medical record abstraction). Two of our main goals were to determine the usefulness of these criteria in identifying strengths and weaknesses of the practices and to provide standards for each criterion for future quality-of-care studies.

As a measure of the appropriateness of prescribing psychotropic drugs, we determined whether commonly accepted clinical indications for the use of these drugs were ever noted in the chart. Almost 100% of patients receiving antidepressants, as opposed to three quarters of users of minor tranquilizers, met this criterion. These findings are consistent with the conclusions of several previous studies (based on patient surveys) that most psychotropic drugs are prescribed for clinically meaningful symptoms.[1,9,11,12] Nevertheless, a quarter of those who received minor tranquilizers did not have an acceptable indication listed in the chart—despite the fact that our criteria included symptoms recorded in progress notes (such as trouble sleeping) as well as diagnoses (depression). Physicians may more carefully document their indications for the use of antidepressants because of concern about the potential side effects of these drugs.

Because of the addictive potential of minor tranquilizers, we were especially interested in the extent of long-term regular use of these drugs. We found that a high proportion (40%) of patients who used minor tranquilizers had long-term regular use. While most long-term users had a reason for that use noted in the chart, we did not evaluate the appropriateness of these reasons. As a result, our estimate of patients who receive "appropriate" care on this criterion is an upper-bound estimate; the lower-bound estimate is the proportion who do not have any long-term use.

The quality-of-care criterion most poorly met by all practices was documentation of a treatment plan. Less than 10% of users of either group of drugs had a plan noted in the chart for discontinuing the drug. This is especially troubling for the use of minor tranquilizers because of the relatively high prevalence of long-term use. Documentation of a treatment plan in the medical record may be especially important in academic settings, where patients are likely to receive care from more than one provider.

Most patients who were started on psychotropic drug therapy during the study period had a follow-up visit scheduled. Further, nearly 80% of patients newly started on an

TABLE 5.—*Antidepressants—Quality-of-Care Criteria*

	Users Meeting the Criterion, Percent*		
		RWJF Group Practices	
Abbreviated Criterion	*BIAC*	*Combined*	*Range Across Practices*
Criterion 1 (indications)			
Depression	100	88	71-100
Any acceptable indication†	100	98	86-100
Criterion 2 (treatment plan)			
1. Other therapy offered	50	50	0-91
2. Purpose stated	0‡	47	0-100
3. Plan for stopping	25	7	0-100
Either 1 or (2 & 3)	50	53	0-100
Criterion 3 (follow-up)§			
Visits scheduled†	100	88	67-100
Return as needed	100	94	80-100
Criterion 4 (follow-up) New prescription only			
Visit occurred within 3 wk	0	42	0-100
within 6 wk	100	78	25-100

*RWJF (funded by the Robert Wood Johnson Foundation) practices have 107 users, BIAC (Beth Israel Ambulatory Care Center) has 4 users.

†The formal criterion.

‡Significantly different from the average of the 15 RWJF group practices combined, $P < .05$.

§New prescription only.

antidepressant regimen (mostly tricyclics) were seen again within six weeks—the recommended interval for an adequate clinical trial of tricyclic antidepressants. Thus, although these providers did relatively poorly in documenting plans for discontinuing drugs, they appeared to be quite concerned (or the patients were concerned) about monitoring the initial period of drug use.

We observed pronounced variation in fulfilling the quality-of-care criteria across the group practices. The variation by practice in quality cannot be explained by differences in demographic characteristics of patients, as the sex and age mix of users of psychotropic drugs was similar among the practices. While we observed large differences among practices in ethnic mix and sources of payment, the particular practices with a high proportion of nonwhites or of patients on public assistance were not necessarily the practices that were significantly different in fulfilling the quality-of-care criteria. In the future, we plan to examine the physician and the patient characteristics that determine the quality of care received using data from a prospective study of patients newly enrolled in the group practices.

Our findings are subject to several limitations. First, the group practices were developed under RWJF grants to provide continuous primary care; they may represent the best available academic internal medicine practices. In fact, the RWJF practices did significantly better than did BIAC, the practice after which they were modeled, on two of five criteria for minor tranquilizer use. Second, we did not study the appropriateness of selecting particular psychotropic drugs or of the dosage prescribed. Consistent with recent recommendations, we opted to focus on the broader style of management with psychotropic drugs.[30] Third, data on quality of care were derived from medical records. Dorsey and associates identified this data source as an appropriate one for such evaluations, however.[20]

In sum, we found that many patients in academic internal medicine group practices have mental health problems and are treated with psychotropic drugs. The style of managing patients with antidepressants appears to be more appropriate than the style of managing with minor tranquilizers. These practices performed well in certain concrete aspects of care, such as scheduling a follow-up visit or avoiding administering minor tranquilizers intravenously or intramuscularly. The practices offered counseling to relatively few patients who used psychotropic drugs and did not set criteria for stopping drugs, even for those who used minor tranquilizers for more than two months.

Thus our quality-of-care criteria were useful for identifying strengths and weaknesses of the care delivered in internal medicine group practices. It may now be appropriate to apply these criteria to other primary care settings, such as family practice clinics.

Further, our results may be useful in focusing peer review efforts or in designing psychiatric consultative services that edueate primary care physicians in managing patients who use psychotropic drugs.

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The Aim of American Medicine Within the Constraints of Today's Society

Beginning in the August 1986 issue the editors of *The Western Journal of Medicine* began a forum for dialogue and discussion of the aim and purpose of medicine within the constraints now being placed on health care. Readers and others are invited to submit their views constructively and succinctly. As many as space permits will be published in future issues of the journal. At an appropriate time all the material will be collated and, if possible, the distillate will be prepared as a statement on "The Aim of American Medicine Within the Constraints of Today's Society."

MSMW

'Your Baby' Medicine

ARNOLD L. SMITH, MD

ONE QUESTION that causes administrators of pediatric hospitals to beat a hasty retreat is "How would you feel if we were cutting corners (that is, costs) and this were your baby?" This query, which is in the same vein as "if this patient were your mother," is rhetorical but I believe it provides an insight into one of the aims of medicine in today's society: namely, patients will still need physicians.

The scenario is becoming familiar. As the amount of money available for health care decreases, hospital administrators will increasingly question, in an economic sense, the rationale of medical practice. Illnesses are reduced to a diagnosis-related group, and a consensus-derived treatment plan is instituted, all within financial guidelines. Competition among a variety of health service institutions has led to "marketing strategies" complete with marketing plans, pep talks for the hospital personnel and ads on the sides of our buses. We've been told that medicine is a business and we need to pay attention to the business of medicine. The formula by which a disease is diagnosed and treated is meshed with accounting practices to yield a dollar amount that is not negative—or even positive if shareholders are involved. After all, if an institution is really providing health care for less, why not make a profit? Contemporary biomedical science has derived the formulae that reduce illness to a series of biochemical events which, on occasion, are still described in physiological terms. People have been taught the power of science and expect it. Good health is a right. No wonder families feel that someone has screwed up when a serious illness occurs to someone close.

When an illness occurs, however, people will still want a physician. They will want a physician to intervene with chemicals or alter the physiology with a scalpel. I contend that people won't be satisfied solely with technical modern medicine, whether it is cost-efficient or profitable or neither. Patients, if not their families, want a physician's attention. And they want a physician as described by Dr Needleman in his Forum piece in the August issue.[1] Are there such physicians available? Certainly there are physicians out there who listen. But requirements for admission to medical school emphasize the physical and natural sciences. The product of this training may be a technician who wishes to work 9 to 5! This ethic fits in well with the medicine "business." In contrast, true physicians throughout history perceive all that is going on with patients. Blending a love of people with authoritative experience and competence, those physicians listen to patients and their families. They perceive not only by reviewing the complete blood count or the social workers' report, but also by "tuning into the wavelength" of patients and their families. Intrinsic human reactions to those perceptions (empathy, concern, sensitivity) expressed in confidence to the patient and family is all the art of medicine—literally fitting it all together.

When the bureaucrats are embarrassed by the question, "would you want me to do it this way if the patient were your baby?", the embarrassment is telling us something. They are telling us that they too know what a physician does. Since they know, we should enlist their aid. Technological innovations will continue to occur and to be more expensive. But society will need physicians to administer this technology in a way not different from the practice of ancient Hindu medicine.[2] Physicians will still need to reconcile algorithmic medicine with a love and respect for the human as a being. The current medical community seems bereft of humanistic physicians. Advertising executives for one HMO in Seattle have recognized this. Their seductive ad says "We listen with more than just a stethoscope" (advertisement by Pacific Health, *Seattle Times*, May 15, 1986, p E7). Academicians, such as myself, should enlist the aid of the health-care bureaucrats to impart in medical students the qualities that were prerequisite for ancient physicians—or to select students with these qualities. Physicians who blend a traditional sense of religion with an understanding of modern technology will be comfortable with the schizophrenic existence, and care for patients. In addition to funding centers for gene therapy, the philanthropic industry should fund a Center for Human Values. I'd wager that, compared with the latest third-generation cephalosporin, the de-

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(Smith AL: 'Your baby' medicine, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Nov; 145:715-716)

velopment costs would be cheap and the benefit a lasting legacy that would profit all of us.

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Patients' Needs at the Center

DAVID LEIGH RODGERS, MD

WHEN A SYSTEM is large, vital and dynamic and it is not functioning well, there is a tendency to make piecemeal changes in it that make matters worse. American medicine is the victim of these good intentions today. Of course, along with medicine the victims include the American people.

The problem is, how do we fix the deficiencies of the medical system without continuing to make it worse? It seems like we are faced with an impossible task. We are overwhelmed by the size, the cost and the pace of the task, and we are, therefore, tempted to make more, small, inadequate alterations.

The fact is, however, the task is quite within our means. No quantum jumps or new inventions are needed to do what must be done, and we have the resources in hand to do it almost overnight. The "constraints" of today's society are self-induced or illusory.

We must change our approach to solutions, however, and we must face facts instead of looking around and under them. In short, we must let go of the past and get a firm grip on today and tomorrow.

Fact number one is that there are tens of millions of people in the United States who do not have health insurance. The reasons they are not insured may be that they are slothful and improvident or they may have changed jobs or been fired or divorced, or they may be self-employed or have a rotten union contract. None of these reasons matter. What does matter, and is unacceptable, is that they are uninsured.

Health insurers would be the first to agree that the healthy pay for the sick, and the larger the program the more predictable and the better it can be. So our response to fact number one must be to create a program of nationwide health insurance, where everyone in the United States has full coverage. Call it national health insurance or socialized medicine; it doesn't matter what it's called as long as it exists.

Fact number two is that some of the main adversaries of nationwide health insurance are the insurance companies because they fear they will lose their business. There is no reason they should lose their business, however. They are the most experienced and best qualified to run a national health insurance system. Their computers and other equipment are in place, their personnel have learned how to recognize abuse and they have every right to profit from their investment and service.

Fact number three is that the governmental bureaucracy is perfectly capable of exercising cost and quality control. In fact, it can do a much better job than it has done with the inefficient mosaic that is in place now and which is rapidly getting worse.

Finally, fact number four is there exists a large, competent medical profession that is capable of providing care to *all* the people if it is given only half a chance.

The application of scientific technologies has led physicians to apply excessive diagnostic and therapeutic interventions, and this has raised costs to unacceptable levels—levels that have incited efforts to mend the system by changing the profession. Good medical care, however, always has included cost containment as a measure of sensible medical judgment. Good sense will again prevail.

But what has happened in the process of mending the medical system is that a crazy quilt has been created that has degraded physicians' self-image and confidence and has removed from them their independence. Physicians are at their best when they are independent. The limitless variables that surround the care of an individual human being require that a physician be free to exercise his or her best judgment for that particular person. Only then can the patient's needs be kept in the center of the medical target.

There are many, many elements of fine tuning that are well known to physicians, medical planners, bureaucrats and lay consumers, and experience and imagination are well within our power to apply.

With the needs of patients at the center of our attention, the aim of American medicine within the constraints of today's society can very happily be met.

Dr Rodgers is a research associate in the Department of Environmental Medicine and International Health, University of California, San Francisco.

(Rodgers DL: Patients' needs at the center, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1986 Nov;145:716)

In Memoriam

California Medical Association

ALWARD, H. CEDRIC, Los Angeles. Died Mar 24, 1986, aged 88. Graduate of McGill University, Montreal, 1924. Licensed in California in 1929. Dr Alward was a member of the Los Angeles County Medical Association.

❦

ATHEY, GEORGE L., Walnut Creek. Died Apr 26, 1986, aged 84. Graduate of Northwestern University, Chicago, 1929. Licensed in California in 1946. Dr Athey was a member of the Fresno-Madera Medical Society.

❦

BAKER, ROBERT S., North Hollywood. Died Mar 20, 1986, aged 58. Graduate of University of California, Irvine, California College of Medicine, 1962. Dr Baker was a member of the Los Angeles County Medical Association.

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BARTLETT, RICHARD J., San Francisco. Died Apr 12, 1986, aged 55. Graduate of University of Michigan Medical School, Ann Arbor, 1955. Licensed in California in 1958. Dr Bartlett was a member of the San Francisco Medical Society.

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BAUERLEIN, THEODORE C., La Jolla. Died Feb 4, 1986, aged 79. Graduate of Cornell University Medical College, New York, 1934. Dr Bauerlein was a member of the San Diego County Medical Society.

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BEAUCHAMP, MARK L., North Hollywood. Died Dec 28, 1985, aged 74. Graduate of University of Alberta Faculty of Medicine, Edmonton, Alberta, Canada, 1937. Licensed in California in 1980. Dr Beauchamp was a member of the Los Angeles County Medical Association.

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BEAVER, HAROLD J., Palo Alto. Died May 8, 1986, aged 93. Licensed in California in 1924. Dr Beaver was a member of the Santa Clara County Medical Society.

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CATALINO, JEROME J., Pacoima. Died Mar 7, 1986, aged 60. Graduate of University of Rome, 1949. Licensed in California in 1958. Dr Catalino was a member of the Los Angeles County Medical Association.

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DALTON, BURR, North Hollywood. Died Mar 3, 1986, aged 79. Graduate of University of Minnesota, Duluth, 1931. Licensed in California in 1937. Dr Dalton was a member of the Los Angeles County Medical Association.

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DAVES, IRA A., Los Angeles. Died Mar 17, 1986, aged 52. Graduate of Howard University College of Medicine, Washington, D.C., 1961. Licensed in California in 1962. Dr Daves was a member of the Los Angeles County Medical Association.

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ELLIOTT, ANNA LUCILLE, Oakland. Died Mar 24, 1986, aged 92. Graduate of University of California, San Francisco, School of Medicine, 1924. Licensed in California in 1924. Dr Elliott was a member of the Alameda-Contra Costa Medical Association.

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ERHARDT, KARL S., South Laguna. Died Feb 11, 1986, aged 68. Graduate of University of Illinois College of Medicine, Chicago, 1942. Licensed in California in 1946. Dr Erhardt was a member of the Los Angeles County Medical Association.

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GARVEY, EDWARD E., Oakland. Died Apr 26, 1986, aged 64. Graduate of Creighton University School of Medicine, Omaha, 1945. Licensed in California in 1945. Dr Garvey was a member of the Alameda-Contra Costa Medical Association.

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HARPER, LESLIE A., Oakland. Died Feb 14, 1986, aged 70. Graduate of University of California, Irvine, California College of Medicine, 1962. Dr Harper was a member of the Alameda-Contra Costa Medical Association.

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HARRIS, JOSEPH M., Los Angeles. Died Feb 7, 1986, aged 87. Graduate of Rush University, Chicago, 1922. Licensed in California in 1922. Dr Harris was a member of the Los Angeles County Medical Association.

Utah State Medical Association

CULLIMORE, LLOYD L., Provo. Died Sep 24, 1986, aged 90. Graduate of George Washington University, Washington, DC. Licensed in Utah in 1926. Dr Cullimore was a member of the Utah County Medical Society.

❦

FRANTZ, MARTHELLA J., Salt Lake City. Died Sep 13,1986, aged 74. Graduate of University of Minnesota. Licensed in Utah in 1965. Dr Frantz was a member of the Salt Lake County Medical Society.

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HICKMAN, GRANT A., Salt Lake City. Died Sep 19, 1986, aged 63. Graduate of University of Utah. Licensed in Utah in 1958. Dr Hickman was a member of the Salt Lake County Medical Society.

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SMITH, SCOTT M., Salt Lake City. Died Jul 15, 1986, aged 73. Graduate of University of Louisville, Kentucky. Licensed in Utah in 1943. Dr Smith was a member of the Salt Lake County Medical Society.

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TANNER, NOALL Z., Layton. Died Jul 10, 1986, aged 76. Graduate of University of Oregon. Licensed in Utah in 1935. Dr Tanner was a member of the Davis County Medical Society.

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WEST, FRANKLIN L., Provo. Died Aug 27, 1986, aged 65. Graduate of University of Utah. Dr West was a member of the Utah County Medical Society.

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cine. UCLA at Santa Monica. Tuesday-Saturday. 33 hrs. Contact: UCLA.

January 23-25—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** Continuing Medical Education Associates at San Diego. Friday-Sunday. 20 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

January 26-28—**Recent Advances in Geriatric Medicine—1987.** UCSD at Holiday Inn Embarcadero, San Diego. Monday-Wednesday. 18 hrs. Fee: $395. Contact: UCSD.

January 28-30—**Neurology for Non-Neurologists.** UCSD at Holiday Inn Embarcadero, San Diego. Wednesday-Friday. 21 hrs. Fee: $375. Contact: UCSD.

January 30-February 1—**Primary Care Update—1987: A Practical Approach.** Scripps Clinic and Research Foundation at Vacation Village Resort, San Diego. Friday-Sunday. Fee: $200. Contact: Bonny Mower, Dept of Academic Affairs, PO Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

February 2-7—**Sexual Science: Bridging the Discipline with the Master Clinicians.** UCLA at Miramar-Sheraton Hotel, Santa Monica. Monday-Saturday. 12 hrs. Fee: $275. Contact: UCLA.

February 4-6—**4th Annual Practical Advances in Medicine.** Cypress Foundation at Carmel Mission Inn, Carmel. Wednesday-Friday. 16 hrs. Contact: Cypress Foundation, PO Box 80308, Salinas 93912. (408) 455-1833.

February 4-7—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Stanford Court Hotel, San Francisco. Wednesday-Saturday. 17 hrs. Contact: UCSF.

February 7-8—**2nd Triennial Diabetes Update.** Cypress Foundation at Hyatt Regency, Monterey. Saturday-Sunday. 10 hrs. Contact: Cypress Foundation, PO Box 80308, Salinas 93912. (408) 455-1833.

February 8-11—**1987 Research Study Club Midwinter Conference.** Sheraton Grande Hotel, Los Angeles. Sunday-Wednesday. Fee: $235-275. Contact: Research Study Club, PO Box J, South Pasadena 91030.

February 9-14—**UCI Family Practice Refresher Course.** UCI at Newport Beach. Monday-Saturday. Contact: UCI.

February 13-15—**Office Gynecology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Islandia Hotel, San Diego. Friday-Sunday. 18 hrs. Fee: $275. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

February 21-28—**Radiology for Emergency and Primary Care Physicians.** Scripps Memorial Hospital, Encinitas at Royal Lahaina Resort, Maui, Hawaii. One week. 21 hrs. Fee: $375. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 23-27—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. Fee: $450.

March 4-6—**37th Annual Course for Physicians in Family Practice: Therapeutic Advances in Family Practice.** Mt Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Robin B. Jackson, Medical Staff and Education Office, Mt Zion Hospital, PO Box 7921, San Francisco 94120. (415) 885-7261.

March 9-13—**Hawaii '87: Critical Issues in Primary Care.** Hawaii Medical Association at Waiohai Hotel, Poipu Beach. Monday-Friday. 20 hrs. Contact: Valerie Murray, Pacfic Institute of Continuing Medical Education, PO Box 1059, Koloa, Kauai, HI 96756. 1 (808) 742-7471.

March 13-15—**Office Emergencies in Primary Care.** Sharp Memorial Hospital at Hotel Del Coronado, Coronado. Friday-Sunday. 18 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

March 16-20—**Epidemics, Pandemics, and Mass Hysteria: From Antiquity to AIDS.** Kauai Foundation for Continuing Education at Poipu Beach, Kauai, Hawaii. Monday-Friday. 19 hrs. Contact: David J. Elpern, MD, Kauai Foundation for Continuing Education, PO Box 3650, Lihue, HI 96766. (808) 245-1507.

March 19-27—**Specialty Series in Primary Care: Cardiology, Infectious Diseases and Endocrinology.** UCSD at Palm Springs Spa Hotel. Thursday-Friday. Contact: UCSD.

March 26-28—**CPR Update/ACLS Recertification.** UCSF at Holiday Inn Union Square, San Francisco. Thursday-Saturday. Fee: $350. Contact: UCSF.

April 20-23—**Selected Topics in Dermatology and Pulmonary Intensive Care.** LLU at LLU. Monday-Thursday. 16 hrs. Fee: $400.

April 25-26—**Transurethral Ureteroscopy: A Seminar and Workshop.** UCSD at La Jolla Marriott Hotel, La Jolla. Saturday-Sunday. 13.5 hrs. Fee: $275-400. Contact: UCSD.

IDAHO

(Continued on Page 726)

FOR HYPERTENSIVE PATIENTS INTOLERANT OF BETA-BLOCKER THERAPY

CONSIDER

VASOTEC®

(ENALAPRIL MALEATE | MSD)

For a Brief Summary of Prescribing Information,
please see last page of this advertisement.

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IT MAY CHANGE THE WA YOUR PATIENTS FEEL O

VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product.

NTIHYPERTENSIVE THERAPY

- Certain subjective symptoms such as malaise and drowsiness, which may interfere with physical or mental activity, have not been characteristic of VASOTEC. This may be related to the specificity of action of VASOTEC on the renin-angiotensin-aldosterone system.
- In worldwide controlled clinical trials, VASOTEC was generally well tolerated. The overall percentage of patients reporting adverse effects was comparable to placebo.
- For the most part, adverse effects in clinical trials were mild and transient and usually did not require discontinuation of therapy.

Angioedema has been reported in patients treated with angiotensin-converting-enzyme inhibitors, including VASOTEC (0.2% of patients treated with VASOTEC). Angioedema associated with laryngeal edema and/or shock may be fatal. **If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately** (see ADVERSE REACTIONS).

Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. Therefore, discontinue therapy with a beta blocker only in accordance with the recommendations in the prescribing information for that product. Begin therapy with VASOTEC on the day following the last day of therapy with the beta blocker.

FOR MANY HYPERTENSIVE PATIENTS
ONCE-A-DAY

VASOTEC®
(ENALAPRIL MALEATE | MSD)

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For a Brief Summary of Prescribing Information, please see next page of this advertisement.

FOR MANY HYPERTENSIVE PATIENTS ONCE-A-DAY

VASOTEC®

(ENALAPRIL MALEATE | MSD)

Contraindications: VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product.

Warnings: *Angioedema:* Angioedema has been reported in patients treated with angiotensin-converting-enzyme inhibitors, including VASOTEC. Angioedema associated with laryngeal edema and/or shock may be fatal. **If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased.

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Neutropenia/Agranulocytosis: Another angiotensin-converting-enzyme inhibitor has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General: Impaired Renal Function:* In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of VASOTEC and/or discontinuation of the diuretic may be required.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia. (See *Drug Interactions*.)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, tongue, difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. (See WARNINGS.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC® (Enalapril Maleate, MSD) is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC may attenuate potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril, but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

There are no adequate and well-controlled studies in pregnant women. VASOTEC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2677 patients.

The most frequent clinical adverse experiences in controlled trials were: headache (4.8%), dizziness (4.6%), and fatigue (2.8%). For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences was not related to total daily dosage within the range of 10 to 40 mg. The overall percentage of patients treated with VASOTEC reporting adverse experiences was comparable to placebo.

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.6%), rash (1.5%), hypotension (1.4%), cough (1.3%), nausea (1.3%), and orthostatic effects (1.3%).

Clinical adverse experiences occurring in 0.5% to 1.0% of patients in the controlled trials included:

Cardiovascular: Syncope, orthostatic hypotension, palpitations, chest pain.

Nervous System: Insomnia, nervousness, paresthesia, somnolence.

Gastrointestinal System: Abdominal pain, vomiting, dyspepsia.

Other: Dyspnea, muscle cramps, hyperhydrosis, impotence, pruritus, asthenia.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema and/or shock may be fatal. If angioedema of the face, tongue, or glottis occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: Combining the results of clinical trials in patients with hypertension or congestive heart failure, hypotension (including postural hypotension and other orthostatic effects) was reported in 2.3% of patients following the initial dose of enalapril or during extended therapy. In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. (See WARNINGS.)

Clinical Laboratory Test Findings:

Hyperkalemia: (See PRECAUTIONS.)

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.)

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in hypertensive patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

In overseas marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

For more detailed information, consult your MSD representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

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Internal Medicine with invasive vascular procedures	9,153
Internal Medicine — no invasive vascular procedures	4,393
Neurology	2,012
Ophthalmology with surgery or laser	6,773
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Pediatrics — General	2,012
Pediatrics — General, with invasive vascular procedures	9,153
Plastic Surgery, board certified	14,991
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Radiology — diagnostic, no coronary angiography	4,393
Radiology — including coronary angiography	9,153
Urology	11,533

*These rates include dues and assessments for a CAP/MPT member with 50 or more months of membership or retroactive coverage (matured rate). CAP/MPT offers coverage limits of $1 million per occurrence with an aggregate of $3 million per year.

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WYOMING MEDICAL SOCIETY

JANUARY 30-31, 1987 • HOLIDAY INN • CODY, WYOMING

1987 WINTER SEMINAR

FRIDAY, JANUARY 30, 1987

8:45- 9:00 AM LEE K. HERMANN, MD
Introduction

9:00- 9:45 AM VERN LAING, MD
Overview of Clinical Immunology

9:45-10:30 AM HENRY N. CLAMAN, MD
Humoral (B-cell) Immunity; Physiology and Pathology

10:30-10:45 AM (Coffee Break)

10:45-11:30 AM HENRY N. CLAMAN, MD
Cellular (T cell) Immunity; Physiology and Pathology

11:30-11:45 AM *Question and Answer Period*

11:45- 2:00 PM (Lunch)

2:00 PM LEE K. HERMANN, MD
(Reconvene)

2:00- 2:45 PM PETER F. KOHLER, MD
Laboratory Evaluation of Patients with Immune Disorders

2:45- 3:30 PM VERN O. LAING, MD
Allergy (Atopy) with Emphasis on Total and Specific IgE Levels in Wyoming and Oklahoma Patients

3:30- 3:45 PM (Coffee Break)

3:45- 4:30 PM PETER F. KOHLER, MD
Auto-immunity; Current Concepts and Diseases

4:30- 4:45 PM LEE K. HERMANN, MD
Question and Answer Period

SATURDAY, JANUARY 31, 1987

9:15 AM LEE K. HERMANN, MD
(Reconvene)

9:15-10:00 AM DAVID L. COHEN, MD
AIDS I; Etiology, Epidemiology and Public Health Aspects

10:00-10:45 AM DAVID L. COHEN, MD
AIDS II; Clinical Manifestations and Therapy

10:45-11:00 AM (Coffee Break)

11:00-11:30 AM VERN LAING, MD
MODERATOR
Roundtable Discussion, Entire Faculty

11:45- 1:30 PM PRESENTATION OF SCIENTIFIC PAPERS BY WMS MEMBERS

FACULTY

Henry N. Claman, MD
Professor of Medicine
Chief, Division of Allergy and Immunology
University of Colorado Medical Center
Denver

David L. Cohen, MD
Assistant Professor of Medicine
Division of Infectious Diseases
University of Colorado Medical Center

Coordinator, AIDS Activities
Denver Disease Control Center
Denver General Hospital

Peter F. Kohler, MD
Professor of Medicine
Tulane University Medical Center
New Orleans

Vern O. Laing, MD
Allergist
Tulsa, Oklahoma

WYOMING Medical Society

For Reservations and Information Contact:
WYOMING MEDICAL SOCIETY
P.O. Box 4009
Cheyenne, WY 82003-4009
Phone (307) 635-2424

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AN OPEN LETTER TO CALIFORNIA PHYSICIANS

Vicodin® is a Schedule III analgesic in California

Dear Doctor,

As a Schedule III drug, prescriptions for Vicodin may be:

- Refilled 5 times within 6 months.
- Telephoned into local pharmacies.
- Written on regular prescription pads. No triplicate pads are necessary.

We regret any inconvenience caused by the inadvertent reclassification of Vicodin in California to a Schedule II status during July and August of this year. This has been rectified by the California assembly.

Vicodin will continue to be sampled per your request. Thank you for your support of Vicodin.

Please continue to specify "Dispense as written" for the original hydrocodone analgesic.

Sincerely,

John La Lota

John La Lota
Product Manager
Vicodin

vicodin® III

Hydrocodone bitartrate 5 mg (Warning: May be habit forming)
with acetaminophen 500 mg

Greater patient acceptance and longer lasting pain relief.

Please see accompanying brief summary.

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5779/9-86

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vicodin®

hydrocodone bitartrate 5 mg (Warning: May be habit forming) with acetaminophen 500 mg

INDICATIONS AND USAGE: For the relief of moderate to moderately severe pain.
CONTRAINDICATIONS: Hypersensitivity to acetaminophen or hydrocodone.
WARNINGS
Drug Abuse and Dependence: VICODIN is subject to the Federal Controlled Substances Act (Schedule III). Psychic dependence, physical dependence and tolerance may develop upon repeated administration of narcotics, therefore, VICODIN should be prescribed and administered with the same caution appropriate to the use of other oral-narcotic-containing medications.
Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on brain stem respiratory centers. Hydrocodone also affects centers that control respiratory rhythm, and may produce irregular and periodic breathing.
Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.
Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.
PRECAUTIONS
Special Risk Patients: VICODIN should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture.
Information For Patients: VICODIN, like all narcotics, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.
Cough Reflex: Hydrocodone suppresses the cough reflex; caution should be exercised when VICODIN is used postoperatively and in patients with pulmonary disease.
Drug Interactions: The CNS-depressant effects of VICODIN may be additive with that of other CNS depressants. When combined therapy is contemplated, the dose of one or both agents should be reduced. The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone. The concurrent use of anticholinergics with hydrocodone may produce paralytic ileus.
Usage in Pregnancy: Pregnancy Category C. Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the human dose. There are no adequate and well-controlled studies in pregnant women. VICODIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose.
Labor and Delivery: Administration of VICODIN to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.
Nursing Mothers: It is not known whether this drug is excreted in human milk, therefore, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS
Central Nervous System: Sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, dizziness, psychic dependence, mood changes.
Gastrointestinal System: Nausea and vomiting may occur, they are more frequent in ambulatory than in recumbent patients. Prolonged administration of VICODIN may produce constipation.
Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported.
Respiratory Depression: (See WARNINGS.)
DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. However, tolerance to hydrocodone can develop with continued use, and the incidence of untoward effects is dose related.
The usual dose is one tablet every six hours as needed for pain. (If necessary, this dose may be repeated at four-hour intervals.) In cases of more severe pain, two tablets every six hours (up to eight tablets in 24 hours) may be required.
Revised: April 1982 5685

KNOLL PHARMACEUTICAL COMPANY
30 NORTH JEFFERSON ROAD, WHIPPANY, NEW JERSEY 07981

5688

(Continued from Page 718)

December 27-January 3—**Internal Medicine.** Sun Valley. One week. Sponsor: University of Washington School of Medicine. Contact: U/W School of Medicine, Division of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 27-March 1—**Personal Fitness for You and Your Patient: Speakers From the Cleveland Clinic.** Shore Lodge, McCall. Friday-Sunday. Sponsor: Ada County Medical Society. 11 hrs. Fee: $125. Contact: Judy Barningham, Ada County Medical Society, PO Box 2668, Boise 83701. (208) 336-2930.

March 14-21—**How to Make Fitness and Health Promotion Work in Your Practice.** Sun Valley. One week. 24 hrs. Sponsors: University of Arizona, Department of Family and Community Medicine, and Epic Medical Expeditions. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley 83353. (208) 788-4995.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

November 14-15—**Behavioral/Physiological Changes of Aging.** Albuquerque. Friday-Saturday. Marriott Hotel. Contact: Lovelace Medical Foundation, Office of Medical Education, 2425 Ridgecrest Dr SE, Albuquerque 87108. (505) 262-7000.

December 4-6—**Annual Meeting—New Mexico Chapter, American College of Physicians/New Mexico Society of Internal Medicine.** Albuquerque. Thursday-Saturday. Marriott. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

December 12-13—**Trauma Update '86.** Albuquerque. Friday-Saturday. UNM Conference Center. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

January 24-25—**Annual Family Practice Seminar.** Albuquerque. Saturday-Sunday. Marriott Hotel. Contact: New Mexico Chapter, American Academy of Family Physicians, PO Box 23070, Albuquerque 87192. (505) 298-5300.

February 5-7—**New Mexico-West Texas Urological Society—Annual Meeting.** Albuquerque. Thursday-Saturday. St Joseph Hospital. Contact: Edward L. Johnson, MD, 7000 Cutler NE, Albuquerque 87110. (505) 883-6230.

February 19-21—**Sports Medicine.** Tammaron. Thursday-Saturday. Contact: Loveless Medical Foundation, Office of Medical Education, 2425 Ridgecrest Dr SE, Albuquerque 87108. (505) 262-7353.

February 20-22—**15th Annual Taos Lung Disease Symposium.** Taos. Friday-Sunday. Contact: NM Chapter, American Thoracic Society, 216 Truman NE, Albuquerque 87108. (505) 265-0732.

February 27-28—**Advances in Internal Medicine VII.** Albuquerque. Friday-Saturday. VAMC Conference Center. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

March 5-7—**20th Annual Ob/Gyn Postgraduate Seminar.** Albuquerque. Thursday-Saturday. Hilton. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

March 11-14—**New Mexico Metabolism Symposium.** Taos. Wednesday-Saturday. Quail Ridge Lodge. Contact: Lovelace Medical Foundation, Office of Medical Education, 2425 Ridgecrest Dr SE, Albuquerque 87108. (505) 262-7353.

March 14—**New Mexico Pediatric Society Wylder Lecture—Pediatric Neurology.** Albuquerque. Saturday. Contact: NM Pediatric Society, (505) 758-8651.

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave, Portland, OR 97201, or phone (503) 226-1555.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

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MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 W Harvard Ave, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 W Harvard Ave, Roseburg 97470. (503) 673-6641.

Emanuel Hospital, 2801 N Gantenbein St, Portland 97227:

Every Friday, 12:15 p.m. to 1:00 p.m. **Medical Grand Rounds.** Contact: Philippa McClure, Emanuel Hospital, 2801 N Gantenbein St, Portland 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Ave, Portland 97210:

Every Tuesday, 12:00 noon to 1:00 p.m. **Medicine Grand Rounds.** Neurological Sciences Buildings, First Floor Auditorium. Contact: Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Ave, Portland 97201. (503) 229-7454.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder St, Eugene 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene 97440.

Salem Hospital, 665 Winter St SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St SE, Salem 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St SE, Salem 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St Vincent Hospital & Medical Center, 9205 SW Barnes Rd, Portland 97225. (503) 297-4411, Ext 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept of Psychiatry, Oregon Health Sciences University, Portland 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept of Medicine, Oregon Health Sciences University, Portland 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland 97201. (503) 225-7590.

EMERGENCY MEDICINE

November 14-15—**Symposium on Critical Care Medicine.** Portland. Thursday-Friday. Red Lion Motor Inn/Jantzen Beach. Contact: OHSU-CME.

FAMILY PRACTICE

February 9-13—**18th Annual Family Practice Review.** Portland. Monday-Friday. Marriott Hotel. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

January 23—**Infectious Disease Symposium.** Portland. Friday. OHSU Campus. Contact: OHSU-CME.

(Continued on Page 730)

Here's the Scoop...

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California Medical Association
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cma

Yes, please send me information on CMA's 1987 Annual Session.

Name _____

Address _____

City _____ State _____ Zip _____

(Continued from Page 728)

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

November 20-21—**Postgraduate Laser Program—GI.** (Sponsor: UUMC). Thursday-Friday. University of Utah Medical Center, Salt Lake City. 10 hrs. Contact: John Dixon, MD, (801) 581-2256.

November 22—**Cognitive Therapy of Phobias and Anxiety Disorders** (Sponsor: UUMC). Saturday. University of Utah Campus, Salt Lake City. 6.5 hrs. Contact: Sandra Jones, (801) 581-5809.

January 5-14—**Hip and Knee Bioskills Workshop** (Sponsor: UUMC). 10 days. Snowbird Resort. 15 hrs. Contact: Aaron Hoffman, MD, (801) 581-8664.

January 20-22—**Pulmonary Function Testing** (Sponsor: UUMC). Tuesday-Thursday. RMCOEH, University of Utah. 18 hrs. Contact: Connie Crandall, (801) 581-8719.

February 1-6—**Diagnostic Imaging/Interventional Radiology** (Sponsor: UUMC). Sunday-Friday. Snowbird Resort. 20 hrs. Contact: Judy Gallegos, (801) 581-8188.

February 9—**Stress, Emotion and Heart Disease** (Sponsor: UUMC). Monday. Westin Hotel Utah, Salt Lake City. 6 hrs. Contact: Hilmon Castle, MD, (801) 581-8664.

February 10-13—**Family Practice Refresher Course** (Sponsor: UUMC). Tuesday-Friday. Westin Hotel Utah, Salt Lake City. 28 hrs. Contact: Denise Denton, (801) 581-5224.

February 11-14—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wednesday-Saturday. Salt Lake City. 17 hrs. Contact: (801) 521-1221.

February 12-14—**Rigid Fixation Techniques/Craniomaxillofacial Surgery** (Sponsor: UUMC). Thursday-Saturday. Snowbird Resort. 20 hrs. Contact: Louis Morales, MD, (801) 581-8664.

February 14-21—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). One week. Park City Resort. 25 hrs. Contact: John Matsen, MD, (801) 581-7480.

February 19-21—**Mid-Winter Trauma Seminar for Military and Civilians** (Sponsor: UUMC). Thursday-Saturday. Westin Hotel Utah, Salt Lake City. 15 hrs. Contact: Clayton Petty, MD, (801) 581-6393.

February 20-24—**Postgraduate Course in Anesthesiology** (Sponsor: UUMC). Friday-Tuesday. Salt Lake City. 16 hrs. Contact: Theodore Stanley, MD, (801) 581-6393.

February 21-25—**Annual Ob-Gyn Update** (Sponsor: UUMC). Saturday-Wednesday. Park City. 15 hrs. Contact: James Scott, MD, (801) 581-5501.

February 22-27—**Park City Dermatology Seminar** (Sponsor: UUMC). Sunday-Friday. Park City. 18 hrs. Contact: Gerald Kruegar, MD, (801) 581-7837.

February 23-27—**Surgical Pathology Workshops** (Sponsor: UUMC). Monday-Friday. The Yarrow, Park City. 20 hrs. Contact: Tom Colby, MD, (801) 581-7480.

February 25-28—**Gynecologic Oncology** (Sponsor:

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143, (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
UVH:	Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

UUMC). Wednesday-Saturday. Park City. 15 hrs. Contact: James Scott, MD, (801) 581-5501.

February 26-28—**Arthroscopic Surgery** (Sponsor: UUMC). Thursday-Saturday. Westin Hotel Utah, Salt Lake City. 21 hrs. Contact: Robert Metcalf, MD, (801) 581-7601.

March 2-6—**Advances in Internal Medicine.** (Sponsor: UUMC). Monday-Friday. Snowbird Resort. 25 hrs. Contact: Malcolm Berenson, MD, (801) 581-7801.

March 8-13—**Diagnostic Imaging and Interventional Radiology** (Sponsor: UUMC). Sunday-Friday. Snowbird Resort. 20 hrs. Contact: Judy Gallegos, (801) 581-8188.

March 9-13—**Medical and Surgical Advances in GI** (Sponsor: UUMC). Monday-Friday. Snowbird Resort. 25 hrs. Contact: Malcolm Berenson, MD, (801) 581-3581.

March 9-14—**Advanced Rheumatology 1987** (Sponsor: UUMC). Monday-Saturday. Snowbird Resort. 20 hrs. Contact: John Ward, MD, (801) 581-8664.

March 11-13—**9th Annual Common Problems in Pediatrics** (Sponsor: UUMC). Wednesday-Friday. Salt Lake Hilton. 14 hrs. Contact: Katharine Blosch, (801) 466-3500.

March 16-20—**Nutrition in Contemporary Medicine** (Sponsor: UUMC). Monday-Friday. Park City. 30 hrs. Contact: Malcolm Berenson, MD, (801) 581-3581.

March 26-28—**Neurology for the Practitioner** (Sponsor: UUMC). Thursday-Saturday. Salt Lake City. 15 hrs. Contact: Richard Baringer, MD, (801) 581-8664.

April 6-8—**Genetic Testing and New Biomedical Technologies in the Prevention of Occupational and Environmental Disease** (Sponsor: UUMC). Monday-Wednesday. Park City. 18 hrs. Contact: Connie Crandall, (801) 581-8719.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

November 21-22—**Short-Term Therapy.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

December 3-5—**Molecular Medicine.** Seattle. Wednesday-Friday. Urban Horticulture Center. Contact: U/W.

December 4-5 —**Worker Health and Safety at Hazardous Waste Site.** Seattle. Thursday-Friday. NW Center for Occupational Health and Safety. Contact: U/W.

December 5—**Practical Pediatrics.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

December 5-6—**Northwest Urologists/Washington State Urology—1986 Annual Meeting.** Tacoma. Friday-Saturday. Tacoma Sheraton. Contact: WSMA.

January 15-16—**Agricultural Health and Safety.** Seattle. Thursday-Friday. NW Center for Occupational Health and Safety. Contact: U/W.

January 23—**Topics in Pulmonary Medicine: Interstitial Lung Disease.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

January 30—**Alternative Delivery and Financing Systems: Your Options and How to Evaluate Them.** Seattle. Friday. Contact: AMA, Dept of Practice Management, 535 N Dearborn St, Chicago, IL 60610. (312) 645-4958.

February 4-6—**Spirometry Training for Worker Screening.** Seattle. Wednesday-Friday. NW Center for Occupational Health and Safety. Contact: U/W.

February 6-7—**Modern Concepts in Allergy.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 7-8—**Vocational Rehabilitation.** Bellevue. Saturday-Sunday. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 623-4801.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

(Continued on Page 736)

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ARIZONA BASED PHYSICIAN RECRUITMENT firm has opportunities Coast to Coast. "Professionals working with Professionals." Over 14 years experience. Call (602) 795-7474; or send CV to: Mitchell & Associates, Inc., 2761 N. Country Club Rd., Ste. 202, Tucson, AZ 85716.

OBSTETRICS AND GYNECOLOGY—multispecialty, family care oriented group has two excellent practice opportunities for OB/GYN specialists. We are located in a growing, dynamic Southwest city and offer an excellent benefit and incentive salary program. Send CV to D. R. Molesworth, Administrator, The Tucson Clinic, P.C., PO Box 26926, Tucson, AZ 85726.

MD NEEDS—SOUTHERN CALIFORNIA ONLY—FPs, GP, IM, OB/GYN, OR and other subspecialties needed for private groups and associations. Baker, Ellerd and Associates, Inc., 16200 Ventura Blvd., Ste. 426, Encino, CA 91436; call (818) 995-4311.

EMERGENCY MEDICINE Career opportunities for primary care physicians are immediately available with Spectrum throughout Arizona. Openings are for emergency department medical directors and full-time staff physicians at select client hospitals in Arizona. You can choose the location and practice situation that meets your needs. Guaranteed competitive rate of compensation, full protection of occurrence malpractice insurance coverage, plus Medical Directors receive paid life, health, disability and dental insurance which includes dependents. For more details on these excellent opportunities in Arizona, contact Bill Salmo, Spectrum Emergency Care, 6275 Lehman Dr., Ste. C202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

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VANCOUVER/CAMAS, WASHINGTON. BC/BE Family Practitioner to join a growing FP department within a well established 30-physician multispecialty group. Satellite clinic is in a high growth area with a multitude of outstanding recreational, cultural and educational opportunities in nearby Portland, Oregon, Mt. Hood, and the Columbia Gorge. High quality practice with excellent vacation and benefits package. Salary first two years, with potential for full partnership. Send CV to: Roger R. Garretson, 700 N.E. 87th Ave., Vancouver, WA 98664.

IMMEDIATE OPENING—Immediate Care Center. Large, multispecialty clinic located in southeastern Washington has an opening for a qualified physician to join a Board certified Emergency Physician in staffing a walk in/immediate care center. Corporate paid retirement plan, excellent compensation package, superior recreational and cultural opportunities in a family-oriented environment. Send complete CV to James Mercer, MD, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362; or call 1-(509) 522-0550.

ALLERGIST/CLINICAL IMMUNOLOGIST (Pediatric and Adult) BE/BC to join a well established allergist working in an 80 plus physician multispecialty group located in California's Central Valley. Within two hours of San Francisco, Yosemite, Carmel and the Sierras. Generous guaranteed base salary with incentive, early partnership. Reply with CV and references to: C. R. Maino, MD, Gould Medical Foundation, 600 Coffee Rd., Modesto, CA 95355.

OTOLARYNGOLOGIST. Position available with 35-member multispecialty group; BC/BE; immediate opening; full range of benefits plus immediate shareholder status; excellent opportunity; central coast of California. Respond with CV to: Colin J. Wells, MD, San Luis Medical Clinic, Ltd., 1235 Osos St., San Luis Obispo, CA 93401-3619. No phone calls please.

CALIFORNIA. BC/BE Pediatrician and Internist to join young group at the edge of the Sierras. Send CV to Number 149, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PHYSICIANS WANTED

BUSY FEMALE GYN looking for quality associate. Excellent opportunity in suburban Los Angeles for BC/BE OB/GYN. Full- or part-time. Gynecology only, but great potential for full Obstetrics practice if desired. Position available immediately. Must be sensitive, well-trained, personable, and hard-working man or woman. Please reply to Number 152, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

INTERNIST BC/BE—Opening for General Internist in a 32-physician, multispecialty group located in the Pacific Northwest. Guaranteed salary and immediate full participation in incentive program, plus outstanding benefit package. Please submit your CV to the Search Committee, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

OREGON—Opportunity for a committed, energetic physician to become a leader in the development of a primary care group practice in Portland, Oregon. Affiliated with a prominent medical center, the practice will open multiple offices offering care which reflects the traditional values of the profession in a competitive manner. Salaried position with bonus, stock options, and excellent benefits. Send CV to: Number 154, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PEDIATRICIAN: The San Luis Medical Clinic, Ltd. a 35-member multispecialty group practicing on the California central coast has an immediate need for a general Pediatrician. Full range of benefits and all practice costs paid. Send CV to: Colin J. Wells, MD, San Luis Medical Clinic Ltd., 1235 Osos St., San Luis Obispo, CA 93401-3619. No telephone calls please.

MINNEAPOLIS—Family Practice, Internal Medicine, Cardiology, Child Psychiatry, Adult Psychiatry, Obstetrics/Gynecology, Ophthalmology. Join established group in one of America's leading metropolitan areas. Group provides professional liability, four weeks vacation, two weeks conference leave, disability, retirement, hospital dues and more. Must be Board certified or Board eligible. Direct inquiries to: Paul J. Brat, MD, Medical Director, Group Health, Inc., 2829 University Ave. SE, Minneapolis, MN 55414.

ARIZONA—VA Medical Center, Prescott, Arizona, Medical Service is recruiting for a full-time, Board certified Geriatrician and/or General Internist. Position available now. Prescott is a 217 bed general medical hospital with an active medical service, ICU/CCU, Ambulatory Care, Rehabilitation Medicine Service, Alcohol Dependency Treatment Program, and intermediate bed care units. Prescott is located in the mountains of North Central Arizona with a population of 25,000. Salary range is $70,000 to $80,000 depending on qualifications. Send curriculum vitae to: F. C. Lepperd, Jr., MD, Chief of Staff, VA Medical Center, Prescott, AZ 86313; or call (602) 445-4860, Ext. 301; Equal Opportunity Employer.

FIRCREST SCHOOL for the developmentally disabled seeks Pediatrician/chronic care. Interdisciplinary team setting. University affiliation encouraged. Submit résumé to R. Doan, MD, Fircrest School, 15230-15th NE, Seattle, WA 98155. Apply Fircrest Personnel, (206) 364-0300, ext. 430, EOE.

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(Continued on Page 734)

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(Continued from Page 732)

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FAMILY PRACTICE. Position available with 35-member multispecialty group; BC/BE; immediate opening; full range of benefits plus immediate shareholder status; excellent opportunity; central coast of California. Respond with CV to: Colin J. Wells, MD, San Luis Medical Clinic, Ltd., 1235 Osos St., San Luis Obispo, CA 93401-3619. No phone calls please.

NEW MEXICO—Primary Care Physician for 600-bed psychiatric/geriatric hospital in Las Vegas, New Mexico. Competitive salaries and generous benefits including on-call compensation. Superb climate and nearby recreational facilities. Contact: Medical Director, Las Vegas Medical Center, PO Box 1388, Las Vegas, NM 87701-1388 or call (505) 425-6711, ext. 5402.

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OB/GYN position available with 35-member multispecialty group; BC/BE; immediate opening; full range of benefits plus immediate shareholder status; excellent opportunity; central coast of California. Respond with CV to: Colin J. Wells, MD, San Luis Medical Clinic, Ltd., 1235 Osos St., San Luis Obispo, CA 93401-3619. No phone calls please.

CHIEF OF INTERNAL MEDICINE (Physician III)—$6,151-$6,504/monthly. Applications are being accepted for the Chief of Internal Medicine with the County Hospital. Natividad Medical Center is a 204-bed teaching hospital affiliated with the University of California, San Francisco for a family practice residency program. Excellence in teaching and administrative experience required along with Board certification. For applications and further information, submit CV to Ray K. Bolinger, Hospital Administrator, Natividad Medical Center, PO Box 8-1611, Salinas, CA 93912-1611; or phone (408) 757-0585. FFD until sufficient applications are received.

B/C-B/E DIAGNOSTIC RADIOLOGIST

Hospital and office practice. All modalities except MRI. Hands on experience in real time ultrasound desired. Excellent salary and benefits, commensurate with experience. Early partnership. Will consider locums. Send CV to Radiology, 5681 N. Fresno St., Fresno, CA 93710; (209)439-2464.

FAMILY PRACTICE OPPORTUNITY. Five person Portland, Oregon, group looking for two new partners. Solid growing practice with HMO and PPO affiliations. First year guarantee plus benefits. Contact: The Friedrich Group, Inc., 9284 Ferncliff NE, Bainbridge Island, WA 98110; (206) 527-3141 or (206) 842-5248.

POSITIONS AVAILABLE

MEDICAL DIRECTOR—Annual salary established to $103,000. Excellent fringe benefits/continuing education program/self-insured. The Los Angeles Department of Water and Power (DWP) is seeking a California licensed MD with increasingly responsible professional and administrative experience in occupational health programs for employment as Medical Director. DWP has over 10,000 employees and an expanding medical program providing entry physicals; medical and minor surgical services; medical consultation on occupational health issues, including Workers' Compensation and OSHA Medical Surveillance through the use of mobile medical vans at statewide DWP facilities. Please submit a résumé, by November 25, 1986 to Mr Jeff Pfau, Manager of Occupational Health and Benefits, Department of Water and Power, 111 N. Hope St., Room 549, Los Angeles, CA 90012. Your résumé, clearly delineating your relevant experience and training, will be accepted in confidence. Questions? Telephone Mr Pfau at (213) 481-4575. The Department of Water and Power is an Equal Opportunity Affirmative Action Employer.

SAN DIEGO

Busy, multispecialty group in San Diego is expanding and will be adding Specialists and Family Physicians to its staff. Outstanding practice opportunities in an ideal geographic setting. For immediate consideration, please send CV to: Miriam Stephens, Director of Professional Recruitment, SMITH HANNA Medical Group, 5703 Oberlin Dr., Ste. 302-49, San Diego, CA 92121.

GENERAL INTERNAL MEDICINE with an emphasis on Cardiology. Private multispecialty clinic in prime urban location in Washington. First year salary guarantee plus incentives and excellent benefits including Pacific Northwest life-style. Contact: The Friedrich Group, Inc., 9284 Ferncliff NE, Bainbridge Island, WA 98110; (206) 527-3141 or (206) 842-5248.

NORTHERN CALIFORNIA, EMERGENCY MEDICINE. Full-time positions available in the Emergency Room at The University of California Davis Medical Center. The University serves a large region of Northern California and is a major trauma center. Emergency physicians teach and supervise medical students and housestaff in addition to treating patients, primarily. Opportunities exist for involvement in other School of Medicine teaching activities. Applicants should send curriculum vitae to Robert W. Derlet, MD, University of California Davis Medical Center, 2315 Stockton Blvd., Department of Emergency Medicine, Trailer 1219, Sacramento, CA 95817.

PRIVATE/NON-PROFIT MULTISPECIALTY GROUP in Hispanic community seeks Board eligible/Board certified Internist, Family Practitioner and Pediatrician to join established group to provide comprehensive ambulatory and in-patient care. Send curriculum vitae to: Community Health Foundation, 3945 E. Whittier Blvd., Los Angeles, CA 90023; (213) 266-4690, Ext. 250—Personnel.

SAN FRANCISCO—ONE HOUR. Multispecialty group which is growing fast is accepting applications for the following specialties: Pediatrician, Pulmonologist, Surgeon, ENT. First year includes salary plus benefits. After one year partnership may be offered. Reply to Number 157, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FAMILY PRACTITIONER to join established 42-year-old Family Practitioner in Garden Grove, California. Part-time to start. Salary guarantee to percentage after one year. Send CV to Number 158, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

TALENTED INTERNIST full-time in private practice with four other Internists covering rural ER/Acute medicine. Involves four two night shifts per month. Scheduling flexible. Sense of humor preferred. 60K. C. Rath, MD, 199 E. Webster St., Colusa, CA 95932; (916) 458-7739.

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PHYSICIAN POSITIONS: Multi-site primary care non-profit corporation is seeking physicians for full- or part-time practice. General Practice, Family Practice, Internal Medicine physicians needed. Competitive salary and excellent benefit package. All inquiries strictly confidential. Contact Jack Hicks, Assistant Director, at (805) 845-3731 for more information or send CV to Clinica Sierra Vista, PO Box 457, Lamont, CA 93241.

PATHOLOGIST: Large pathology group in greater Los Angeles area seeking qualified Anatomic and Clinical Pathologist. Prefer applicants with fellowship training or 1-2 years experience. Excellent position with growth potential. Send résumé to: Glenview Pathology Medical Group, 9331 Venice Blvd., Culver City, CA 90230, Attn: Dr Emanuel Abrams.

FAMILY PRACTICE PHYSICIAN/MEDICAL DIRECTOR. (Scenic Northwest) Two positions available: Family Practice Physician and Physician/Medical Director. Must be Family Practice physician BC/BE. System of four primary care community clinics. Full-scope family practice, hospital and SIF privileges. New facilities, excellent salary and fringes. Send résumé to: Community Health Care Delivery Systems FC-3312, 3629 South D St., Tacoma, WA 98408. EOE.

PUGET SOUND/WASHINGTON. Pediatrician sought for busy multispecialty urban group practice near children's hospital. Current experience in Pediatrics and newborn intensive care needed. Competitive income and benefit package. Send CV or call: The Friedrich Group, Inc., 9284 Ferncliff NE, Bainbridge Island, WA 98110; (206) 842-5248 or (206) 527-3141.

EPIDEMIOLOGICAL HEALTH ANALYZER—Minimum one year experience with BS degree either field of epidemiology, health, parasitology or related field to assist this medical group in investigating various types of epidemic contagious diseases prevalent within Southern California. Will analyze such information as how many persons in certain areas were affected, how rapid a spread, localities where the diseases became a sudden prevalence, etc. Salary $28,200 per year. Send résumé to: Westmoreland Medical Group, 3030 W. 6th St., Los Angeles, CA 90020; Attn: Dr Song.

FAMILY PHYSICIAN, BC or BE, residency-trained, to join two very busy young FP's in Phoenix, Arizona, July 1987. No OB. Excellent income. Great city. 310 days of sunshine. Contact G. A. Rada, MD, 12251 N. 32nd St., Ste. 4, Phoenix, AZ 85032; (602) 992-1900.

HAWAII. ER PHYSICIAN NEEDED. Full-time, permanent, career position on Kauai. Part of 36-physician multispecialty group. Salary $50-$70K, plus vacation, CME, and complete benefit package. 1,000 visits/month. Full stockholder in 1-2 years. Six ER physicians share shifts evenly. Surfing, diving, fishing, hunting, rodeo, sailing, windsurfing, dirt-biking and polo. Tail covered 100% at end of 5 years. This is a peach, don't hesitate. (Board eligible strongly preferred.) Please submit CV to: James Scamahorn, MD, Kauai Medical Group, 3420-B Kuhio Highway, Lihue, HI 96766. Phone: (808) 245-1012.

PHYSICIANS WANTED. Physicians, BC/BE needed immediately to join expanding multispecialty group. Practice in rapidly growing Southwest community (population 500,000+). Fee-for-service and prepaid health care. Group includes Family Practice/Pediatrics, Internal Medicine/Subspecialties/24 hour Urgent Care. Teaching appointment. Position offers excellent compensation and benefits plus full pension and profit sharing. Relocation expenses. Interested individuals should reply with curriculum vitae to: Southwest Medical Associates, 333 N. Rancho Dr., Ste. 100, Las Vegas, NV 89106.

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SAN FRANCISCO—1 year Fellowship in Psychosomatic Medicine and Consultation Liaison Psychiatry offered by St. Mary's Medical Center, a 550 bed private teaching hospital. Supervised clinical, teaching, and administrative experience in unique Med-Psych inpt unit, Med-Surg wards, Psychiatry and Medicine Clinics, and Sleep Disorders Center. Board eligibility in Psychiatry, Neurology or Medicine required. Contact: D. Nevins, MD, St. Mary's Medical Center, 450 Stanyan St., San Francisco, CA 94117.

SAN FRANCISCO, EMERGENCY MEDICINE. Part-time and full-time positions available in busy emergency department (32,000 patient visits/year) in full service hospital with excellent in-house specialty back-up. Prefere ABEM or ABIM certified/eligible, experienced Emergency Physician. Competitive salary, excellent benefits. Call or write Pat Salber, MD, Kaiser Permanente Medical Group, 2200 O'Farrell St., San Francisco, CA 94115; (415) 929-4020.

PHYSICIAN, full-time, fee-for-service, Pacific Bell Medical Program. Will require assignments in San Ramon or San Jose area. Send CV to Martha Balabegians, MD, 2600 Camino Ramon, Room 1W001, San Ramon, CA 94583.

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CALIFORNIA: Openings for emergency department Medical Directors and full-time staff physicians are immediately available at two client hospitals in California. Guaranteed rate of compensation, occurrence malpractice insurance coverage, flexible scheduling, CME allowance, plus more. For additional details contact Bill Salmo, Spectrum Emergency Care, 6275 Lehman Dr., Ste. C202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

MEDICAL DIRECTOR OF ADOLESCENT CHEMICAL DEPENDENCY PROGRAM—Marshal Hale Memorial Hospital currently seeks a physician (background in internal medicine or general practice preferred) to provide medical leadership, evaluation and patient care for our 20-bed unit. Successful applicant should have experience in the treatment of chemical dependency and/or experience with adolescents. Please send résumé to: Nicholas Talone, Vice President, Professional Services, Marshal Hale Memorial Hospital, 3773 Sacramento St., San Francisco, CA 94118; (415) 666-7837.

GASTROENTEROLOGIST—BC/BE for multispecialty group downtown San Francisco. Send CV and references to: 757 Sutter Medical Clinic, Ste. 100, San Francisco, CA 94109.

ACADEMIC EMERGENCY MEDICINE—The University of California, Davis, School of Medicine is recruiting for a full-time faculty position at the Assistant or Associate Professor level to serve in the Division of Emergency Medicine and Clinical Toxicology. The UCD Emergency Department provides comprehensive emergency care and is a major trauma center. Candidates must be Board certified in Emergency Medicine or Internal Medicine with experience in emergency medicine, and be eligible for licensure in California. The candidate must have prior academic and clinical experience in emergency medicine. Experience in clinical toxicology is highly desirable. A letter outlining research, teaching background and interests, experience, a curriculum vitae and the names of five references must be received by February 28, 1987. Reply to: Robert W. Derlet, MD, Chair of Emergency Medicine Search Committee, Department of Internal Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd., Sacramento, CA 95817. The University of California is an Affirmative Action/Equal Opportunity Employer.

PHYSICIANS WANTED

URGENT CARE CENTER. Arizona, Phoenix and Tucson areas. Opportunity for physician with Family Practice or IM background in hospital-affiliated urgent care centers. Please send CV to: Executive Director—Urgent Care, Mercy Services Corporation-Phoenix, 350 W. Thomas Rd., Phoenix, AZ 85013.

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. . . offers coverage for vacation or continuing education. To arrange coverage for your practice or to participate as temporary physician, contact: **Carol Sweig, Director, 1315 Evans Avenue, San Francisco, CA 94124; (415) 826-7676.**

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BOARD CERTIFIED INTERNIST completing two year Fellowship in Critical Care Medicine. Competent in all ICU procedures. Looking for position as Intensivist in medical or med./surg. ICU in California, Arizona, Oregon or Colorado. Available July 1987. Please reply to Number 156, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PEDIATRICIANS—Husband and wife, are looking for 1 or 2 positions starting August 1987. Prefer Northern California but considering all options. Write Number 159, Western Journal of Medicine. PO Box 7602, San Francisco, CA 94120-7602.

GENERAL VASCULAR SURGEON, certified ABS, GVS; FACS, California licensed. Seeking association at least 80% peripheral vascular. Will consider multispecialty group. Reply Number 160, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SEMINARS

THE AMERICAN ASSOCIATION OF ORTHOPAEDIC MEDICINE presents "Diagnostic Models of Musculoskeletal Pain," May 12-17, 1987, Montreal, Canada. Contact: Deborah Staller, Exec. Sec., AAOM, 926 E. McDowell Rd., Ste 202, Phoenix, AZ 85006; (602) 254-5315.

PRACTICES AVAILABLE

FOR SALE—Well established internal medicine practice. Two offices—Los Angeles and Beverly Hills. Gross $300,000 plus. $100,000 down and additional $25,000/year for 4 years. Qualified buyers only. Please reply to Number 144, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

BUSY GP, SOLO, Northern California wants to retire. Ideal for GP, FP, or Internist. Will sell equipment, furniture and accounts. Will assist with transition. Write or call Edgar Fortner, MD, 2767 Olive Highway, #10, Oroville, CA 95966; (916) 533-7226.

CALIFORNIA: Family,OB/GYN, Pediatrics, Internal, Dermatology, Gastroenterology, Ophthalmology, Neurology, Neurosurgery, Orthopedics, plus many others. Bradshaw Associates, Practice Broker/Recruitment/Valuations, 21 Altamount Dr., Orinda, CA 94563; (415) 376-0762.

FOR SALE—Internal Medicine Practice—Modesto, California. Grosses over $200K. Excellent terms available. Call Mike Page, RH+ Medical Group, Inc. (713) 496-7777.

THIRTY-YEAR-OLD FAMILY PRACTICE for sale. "Silicon Valley's Finest." Approximately 1,000 active patient charts. Mix of 70% private, 30% (over 65). Complete practice and furnishings. Great location in heart of Silicon Valley. Excellent assumable lease. Contact Bugati Royale, 300 Third St., Ste. 4, Los Altos, CA 94022 or call (415) 941-5500.

MOSTLY GERIATRIC PRACTICE for sale in a growing area in beautiful Capitola by the sea (California). Opportunity for rheumatologist. Immediate sale. Equipment available. Will assist in transition. Please reply to Number 146, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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CALIFORNIA PRACTICES FOR SALE. All specialties available. Confidentiality maintained. Request free monthly publication. Appraisals. Financing. Contact PSL (714) 771-4331, (213) 934-0515, (619) 234-9515.

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OFFICE TO SUBLEASE—Santa Monica, Wilshire Boulevard. Can accommodate most specialties. Ideal for Plastic, Ent, Eye. Reasonable rent for area. Reply to Number 125, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

OFFICE FOR SALE—1,200 square feet located in Doctor's Village Medical Complex in beautiful Flagstaff, Arizona. This office is located within 2 blocks of the Flagstaff Medical Center and is perfect for a one man practice. Attractive financing package. Call (602) 779-5335; 9 am to 4 pm. Dr Michael J. Keberlein, 1360 North Rim Dr., Flagstaff, AZ 86001.

OFFICE SPACE FOR SALE OR LEASE. Close to hospitals, downtown. Can accommodate most practices. Large patient waiting area. Contact: William A. Bohart, MD, 960 East First South, Ste 101, Salt Lake City, UT 84102; (801) 532-1164.

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LASER FOR SALE—Coherent Model 450 surgical CO_2, 25 watts, excellent condition, warranty, $20,500. Other medical lasers sold, purchased, reconditioned. Moorpark Electro-optics, Clint Harper, PhD, (805) 529-1649.

SERVICES

INVESTMENT OPPORTUNITIES AVAILABLE. Lab-Net, Inc., a California based clinical lab consulting corporation specializing in the development, management and staffing of physician-owned medical labs, is currently developing several "Shared Physician's Laboratories" throughout California and the United States. Payback on investments are realized in 6 months. Return on investments are over 200% the first year. For details call: (916) 648-2813 in Sacramento or (805) 257-1917 in Los Angeles.

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March 16-20, 1987

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For further information contact:
Dr David J. Elpern,
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CONTINUING MEDICAL EDUCATION

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February 20-21—**Office Gynecology for the Primary Care Physician.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 26-27—**Health and Safety of Firefighters.** Seattle. Thursday-Friday. NW Center for Occupational Health and Safety. Contact: U/W.

March 13--**Recent Developments in Occupational Medicine.** Seattle. Friday. NW Center for Occupational Health and Safety. Contact: U/W.

March 20—**Neuro-Opthalmology Seminar.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

March 30-April 10—**Rehabilitation Review.** Seattle. Monday-Friday. Stouffer Madison Hotel. Contact: U/W.

April 15-16 —**Introduction to Industrial Hygiene.** Seattle. Wednesday-Thursday. NW Center for Occupational Health and Safety. Contact: U/W.

April 17—**Basic Monitoring Laboratory.** Seattle. Friday. NW Center for Occupational Health and Safety. Contact: U/W.

April 25—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 8—**Current Issues in Asbestos Control.** Seattle. Friday. NW Center for Occupational Health and Safety. Contact: U/W.

May 20-22—**Family Violence.** Seattle. Wednesday-Friday. Seattle Center. Contact: U/W.

WYOMING

February 28-March 7—**Selected Topics in Wilderness and Environmental Medicine.** A nordic skiing adventure at Yellowstone National Park. One week. Sponsors: University of Arizona, Department of Family and Community Medicine, and Epic Medical Expeditions. 24 hrs. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995. ◆

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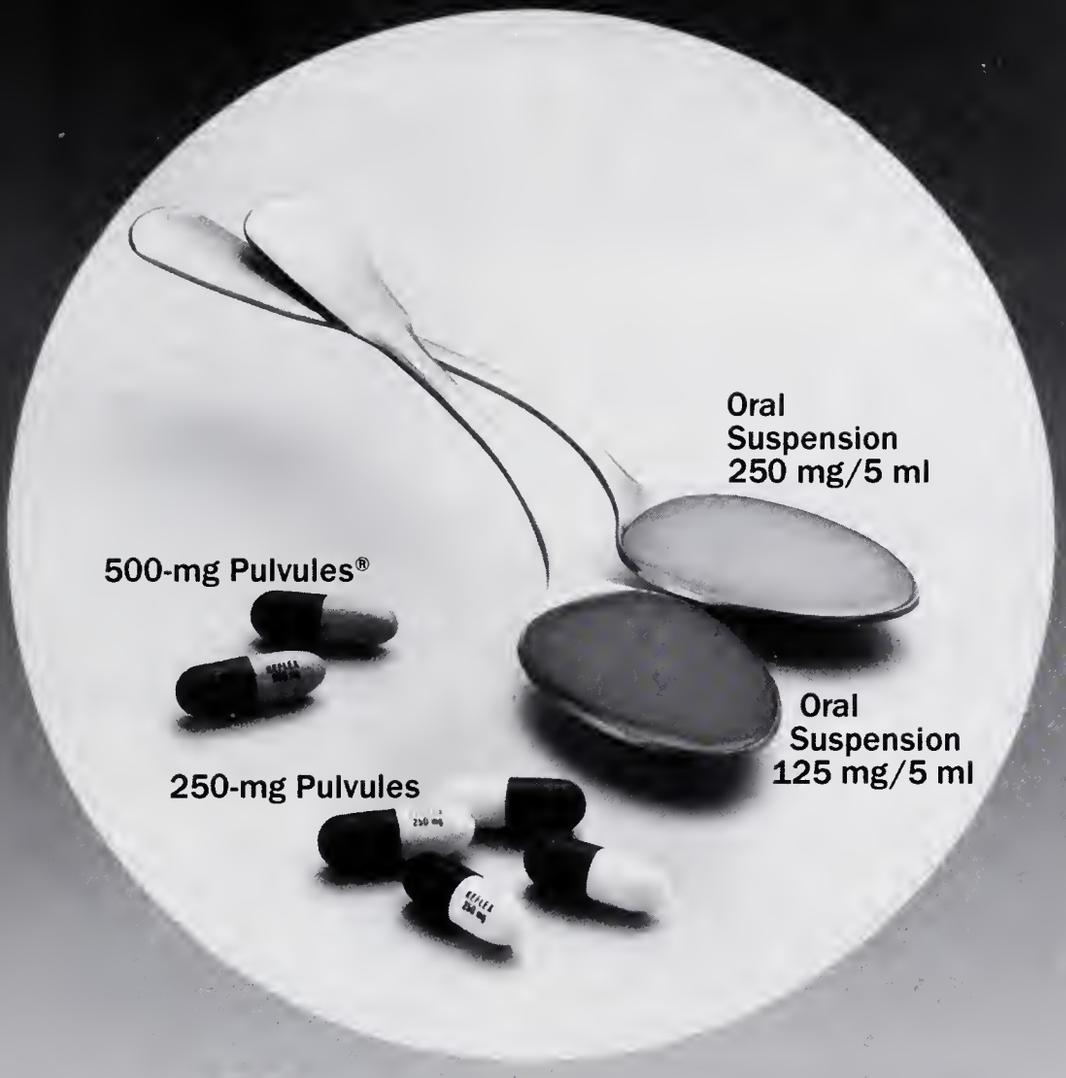

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WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

Alaska State Medical Association—4107 Laurel St, Anchorage 99504. (907) 562-2662. Annual Meeting: June 3-7, 1987, Juneau.

Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 4-6, 1987, Pointe South Mountain, Phoenix.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 863-5522. Annual Meeting: March 6-11, 1987, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1987: Date and place to be announced.

Hawaii Medical Association—320 Ward Ave, Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1986, Westin Ilikai Hotel, Honolulu.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 27-August 2, 1987, Coeur d'Alene.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Interim Meeting: April 3-4, 1987, Colonial Inn, Helena.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 30-May 3, 1987, Ormsby House, Carson City.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 6-8, 1987, Clarion Four Seasons, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): April 3-4, 1987, Salishan Lodge, Lincoln City.

Utah State Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1987: Date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: 1987: Date and place to be announced.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 25-29, 1987, Jackson Lake Lodge, Moran.

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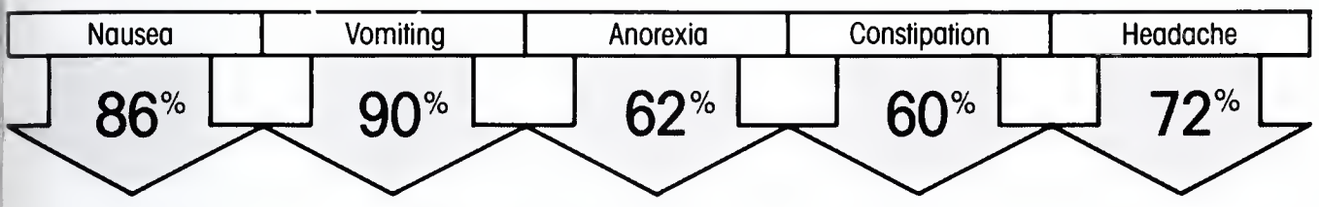

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More than three times as many amitriptyline patients as Limbitrol patients dropped out of therapy because of side effects, although the incidence of side effects was similar. Caution patients against the combined effects of Limbitrol with alcohol or other CNS depressants and about activities requiring complete mental alertness, such as operating machinery or driving a car. In general, limit dosage to lowest effective amount in elderly patients.

References: 1. Data on file, Hoffmann-La Roche Inc., Nutley, NJ **2.** Feighner JP, *et al. Psychopharmacology 61* 217-225, Mar 22, 1979

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Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady state concentrations of the tricyclic drugs. Concomitant use of Limbitrol with other psychotropic drugs has not been evaluated, sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol DS (double strength) Tablets, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol Tablets, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: *Double strength (DS) Tablets,* white, film-coated, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt), and *Tablets,* blue, film-coated, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt). Available in bottles of 100 and 500, Tel-E-Dose® packages of 100, Prescription Paks of 50.

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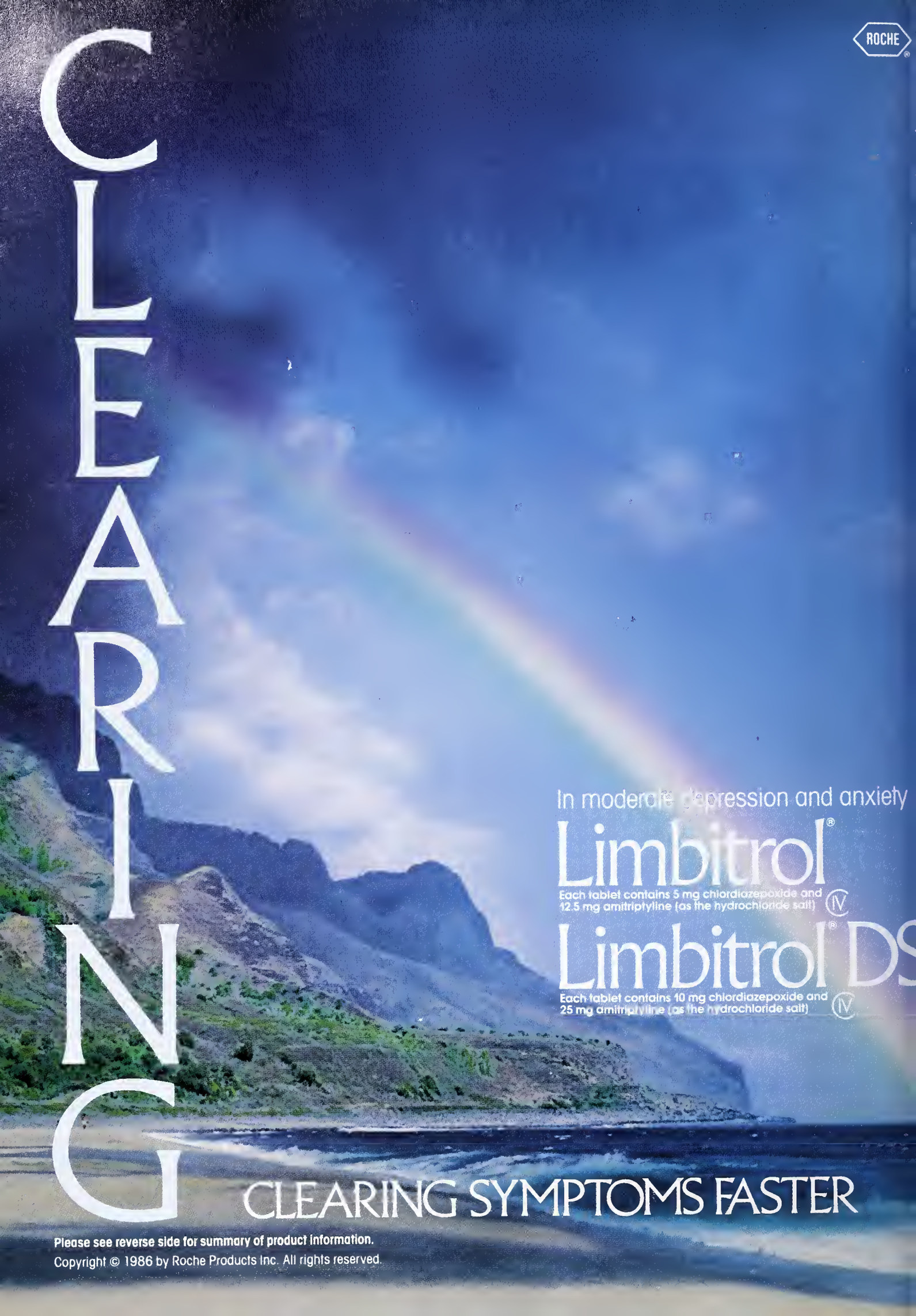

Please see reverse side for summary of product information.

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The Western Journal of Medicine

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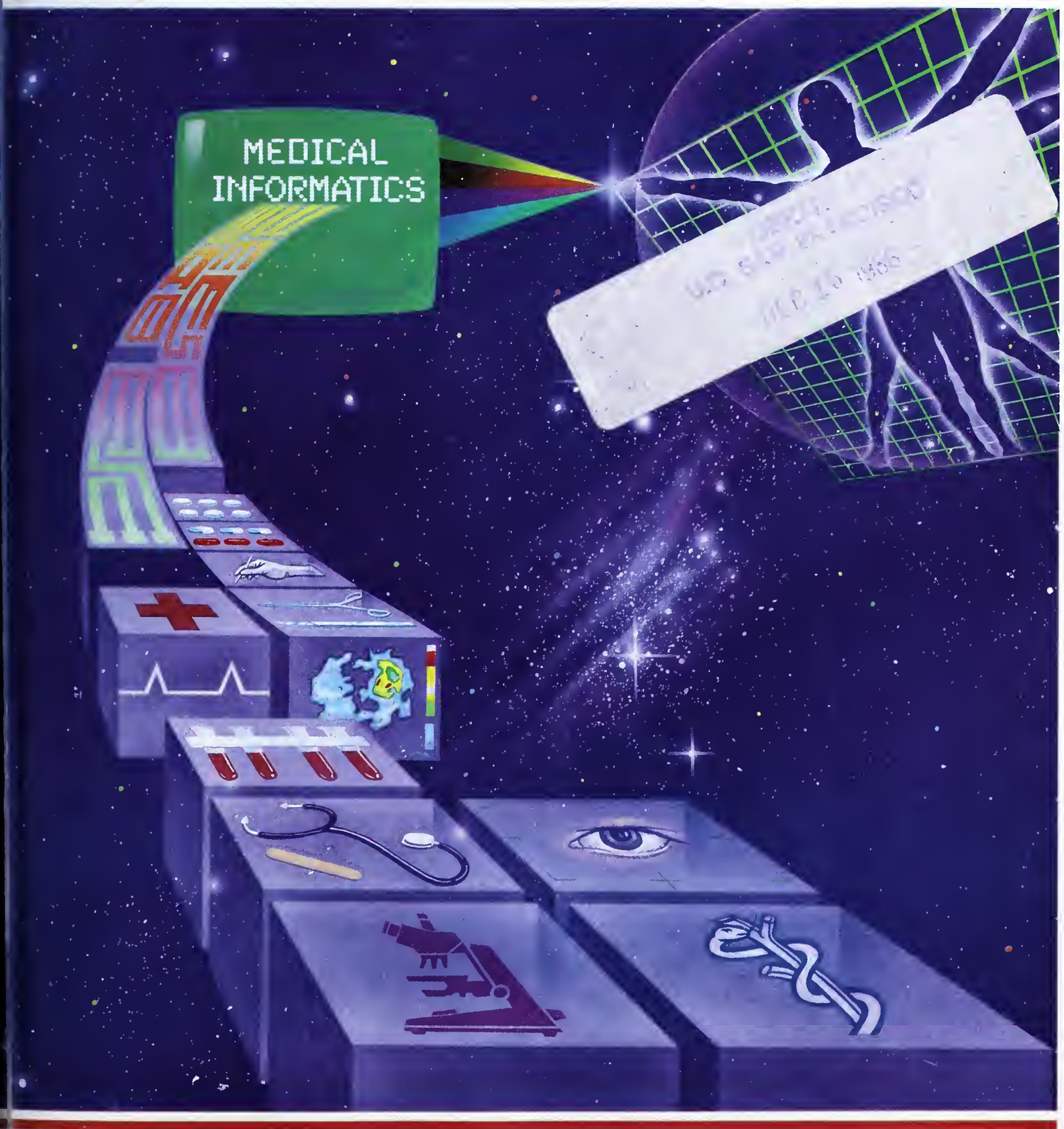

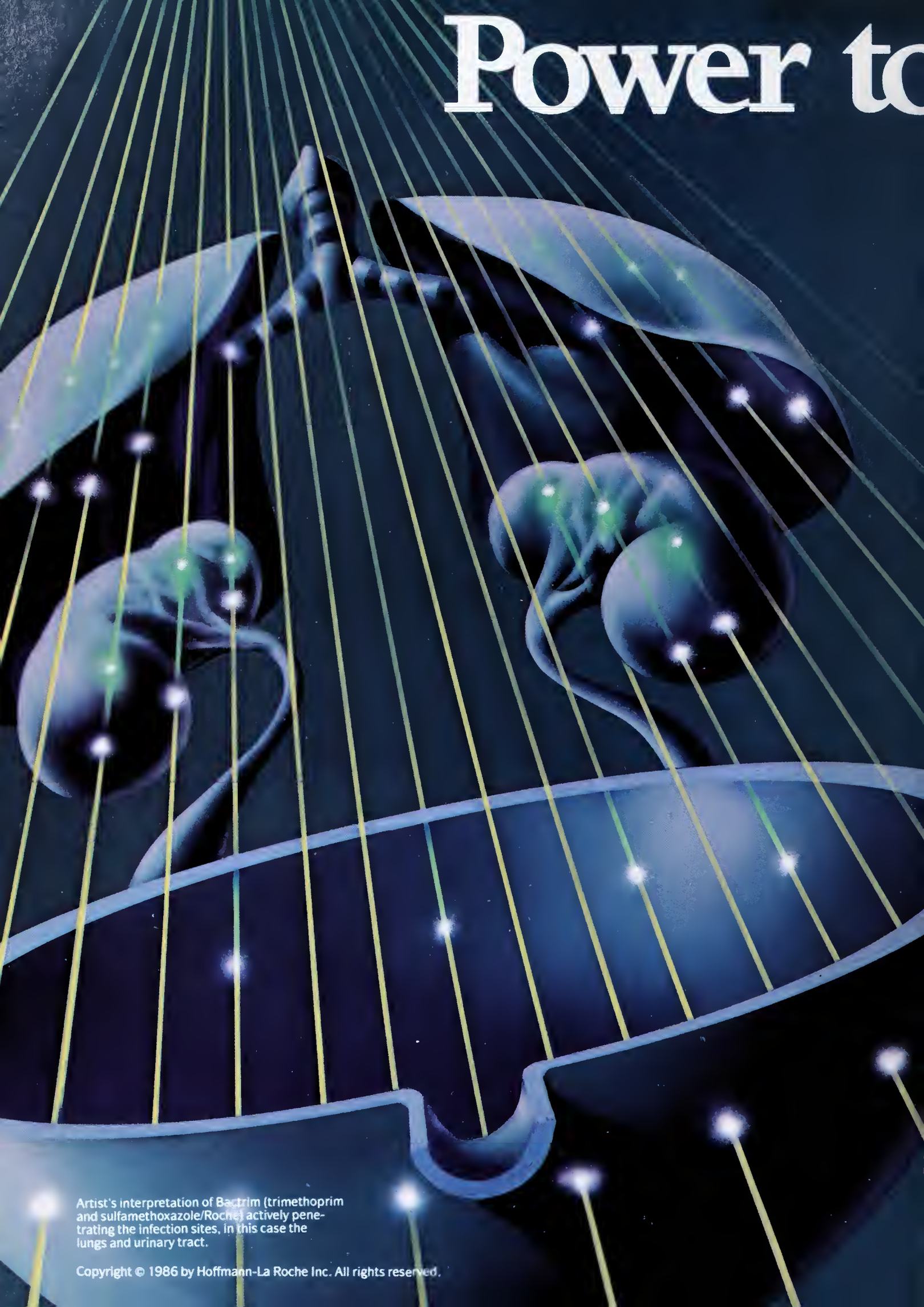

Artist's interpretation of Bactrim (trimethoprim and sulfamethoxazole/Roche) actively penetrating the infection sites, in this case the lungs and urinary tract.

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overpower

he power of penetration into infected tissues and fluids
he strong penetrating power of Bactrim into tissues and fluids is a real benefit in the treatment of acute exacerbations of chronic bronchitis, recurent urinary tract infections and acute otitis media when caused by susceptible strains of pathogens.

he power of concentration through high levels t the site of infection...
n infections like these, Bactrim concentrates its full antibacterial powers at he site of infection, such as the bronchioles or urinary tract.

nd effective levels at the source of reinfection
Bactrim also penetrates into nearby tissues and fluids, often inhibiting the growth of bacterial colonies that might serve as the foci of future infections.[1,2]

he power of spectrum through broad-range activity
Bactrim has proven effective *in vitro* against a broad range of pathogens, ncluding *E. coli, Klebsiella pneumoniae, Enterobacter* and *Proteus* (as in ecurrent urinary tract infections); *S. pneumoniae* and *H. influenzae* (as in cute exacerbations of chronic bronchitis and acute otitis media). After years f use, little change in bacterial resistance has been seen.[3] And Bactrim has ven been reported effective against various ampicillin-resistant strains *in itro*.[4] However, *in vitro* data do not necessarily correlate with clinical results.

.I.D. convenience and economy
ome additional benefits: The convenience of *b.i.d.* dosage and economy are lesigned to encourage patient compliance.

Adequate fluid intake should be maintained during therapy. Bactrim is ontraindicated in infants less than two months, in pregnancy at term, during actation and in patients with documented megaloblastic anemia due to olate deficiency.

pecify Bactrim DS
o be certain your patients get the brand and results you want for them, pecify Bactrim DS and "No Generic Substitution," following your state egulations.

eferences: 1. Rubin RH, Swartz MN: *N Engl J Med 303*:426-432, Aug 21, 1980. 2. Stamey TA, Condy M: *J Infect Dis 131*:261-266, ar 1975. 3. BAC-DATA Medical Information Systems, Inc., Volume II, 1985. 4. Data on file, Hoffmann-La Roche Inc., Nutley, NJ.

Specify. Do Not Substitute.

Bactrim™ DS

160 mg trimethoprim and
800 mg sulfamethoxazole/Roche)

t keeps its powers.

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Please see summary of product information on following page.

BACTRIM™ (brand of trimethoprim and sulfamethoxazole/Roche)

Before prescribing, please consult complete product information, a summary of which follows:
CONTRAINDICATIONS: Hypersensitivity to trimethoprim or sulfonamides; documented megaloblastic anemia due to folate deficiency; pregnancy at term and during the nursing period; infants less than two months of age.
WARNINGS: FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS.
BACTRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. Clinical signs, such as rash, sore throat, fever, pallor, purpura or jaundice, may be early indications of serious reactions. In rare instances a skin rash may be followed by more severe reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis or serious blood disorder. Perform complete blood counts frequently.
BACTRIM SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Bactrim than with penicillin.
PRECAUTIONS: *General:* Give with caution to patients with impaired renal or hepatic function, possible folate deficiency (*e.g.*, elderly, chronic alcoholics, patients on anticonvulsants, with malabsorption syndrome, or in malnutrition states) and severe allergies or bronchial asthma. In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur, frequently dose-related.
Use in the Elderly: May be increased risk of severe adverse reactions in elderly, particularly with complicating conditions, *e.g.*, impaired kidney and/or liver function, concomitant use of other drugs. Severe skin reactions, generalized bone marrow suppression (see WARNINGS and ADVERSE REACTIONS) or a specific decrease in platelets (with or without purpura) are most frequently reported severe adverse reactions in elderly. In those concurrently receiving certain diuretics, primarily thiazides, increased incidence of thrombocytopenia with purpura reported. Make appropriate dosage adjustments for patients with impaired kidney function (see DOSAGE AND ADMINISTRATION).
Use in the Treatment of Pneumocystis Carinii *Pneumonitis in Patients with Acquired Immunodeficiency Syndrome (AIDS):* Because of unique immune dysfunction, AIDS patients may not tolerate or respond to Bactrim in same manner as non-AIDS patients. Incidence of side effects, particularly rash, fever, leukopenia, with Bactrim in AIDS patients treated for *Pneumocystis carinii* pneumonitis reported to be greatly increased compared with incidence normally associated with Bactrim in non-AIDS patients.
Information for Patients: Instruct patients to maintain adequate fluid intake to prevent crystalluria and stone formation.
Laboratory Tests: Perform complete blood counts frequently; if a significant reduction in the count of any formed blood element is noted, discontinue Bactrim. Perform urinalyses with careful microscopic examination and renal function tests during therapy, particularly for patients with impaired renal function.
Drug Interactions: In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Bactrim may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. Keep this in mind when Bactrim is given to patients already on anticoagulant therapy and reassess coagulation time. Bactrim may inhibit the hepatic metabolism of phenytoin. Given at a common clinical dosage, it increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When giving these drugs concurrently, be alert for possible excessive phenytoin effect. Sulfonamides can displace methotrexate from plasma protein binding sites, thus increasing free methotrexate concentrations.
Drug/Laboratory Test Interactions: Bactrim, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs if methotrexate is measured by a radioimmunoassay (RIA). The presence of trimethoprim and sulfamethoxazole may also intertere with the Jaffé alkaline picrate reaction assay for creatinine, resulting in overestimations of about 10% in the range of normal values.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: Long-term studies in animals to evaluate carcinogenic potential not conducted with Bactrim. *Mutagenesis:* Bacterial mutagenic studies not performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim demonstrated to be nonmutagenic in the Ames assay. No chromosomal damage observed in human leukocytes *in vitro* with sulfamethoxazole and trimethoprim alone or in combination, concentrations used exceeded blood levels of these compounds following therapy with Bactrim. Observations of leukocytes obtained from patients treated with Bactrim revealed no chromosomal abnormalities. *Impairment of Fertility:* No adverse effects on fertility or general reproductive performance observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole.
Pregnancy: Teratogenic Effects: Pregnancy Category C. Trimethoprim and sulfamethoxazole may intertere with folic acid metabolism, use during pregnancy only if potential benefit justifies potential risk to fetus. Nonteratogenic Effects: See CONTRAINDICATIONS section.
Nursing Mothers: See CONTRAINDICATIONS section.
Pediatric Use: Not recommended for infants under two months (see INDICATIONS and CONTRAINDICATIONS sections).
ADVERSE REACTIONS: Most common are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria). **FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS (SEE WARNINGS SECTION)** *Hematologic:* Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia. *Allergic Reactions:* Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schoenlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash. Periarteritis nodosa and systemic lupus erythematosus have been reported. *Gastrointestinal:* Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia. *Genitourinary:* Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria. *Neurologic:* Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache. *Psychiatric:* Hallucinations, depression, apathy, nervousness. *Endocrine:* Sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents; cross-sensitivity may exist. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. *Musculoskeletal:* Arthralgia, myalgia. *Miscellaneous:* Weakness, fatigue, insomnia.
DOSAGE AND ADMINISTRATION: Not recommended for use in infants less than two months of age.
URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN: *Usual adult dosage* for urinary tract infections is one DS tablet, two tablets or four teaspoonfuls (20 ml) *b.i.d.* for 10 to 14 days. Use identical daily dosage for 5 days for shigellosis. *Recommended dosage for children* with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses every 12 hours for 10 days. Use identical daily dosage for 5 days for shigellosis. *Renal Impaired:* Creatinine clearance above 30 ml/min, give usual dosage; 15-30 ml/min, give one-half the usual regimen, below 15 ml/min, use not recommended.
ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS: Usual adult dosage is one DS tablet, two tablets or four teasp. (20 ml) *b.i.d.* for 14 days.
PNEUMOCYSTIS CARINII PNEUMONITIS: Recommended dosage is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.
HOW SUPPLIED: *DS (double strength) Tablets* (160 mg trimethoprim and 800 mg sulfamethoxazole)—bottles of 100, 250 and 500; Tel-E-Oose™ packages of 100; Prescription Paks of 20. *Tablets* (80 mg trimethoprim and 400 mg sulfamethoxazole)—bottles of 100 and 500; Tel-E-Oose™ packages of 100; Prescription Paks of 40. *Pediatric Suspension* (40 mg trimethoprim and 200 mg sulfamethoxazole per teasp.)—bottles of 100 ml and 16 oz (1 pint). *Suspension* (40 mg trimethoprim and 200 mg sultamethoxazole per teasp.)—bottles of 16 oz (1 pint).
STORE TABLETS AT 15°-30°C (59°-86°F) IN A DRY PLACE PROTECTED FROM LIGHT. STORE SUSPENSIONS AT 15°-30°C (59°-86°F) PROTECTED FROM LIGHT.

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A better alternative for hypertensives who are going bananas...

Spare your patients the extra cost—in calories, sodium and dollars.

Spare your patients the rigors of dietary K^+ supplementation.

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25mg Hydrochlorothiazide/**50mg** Triamterene/SKF

Effective antihypertensive* therapy...without the bananas

* Not for initial therapy. See brief summary.

Before prescribing, see complete prescribing information in SK&F CO. literature or PDR. The following is a brief summary.

WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: *Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.*

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. *If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake.* ***Associated widened QRS complex or arrhythmia requires prompt additional therapy.*** *Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.*

Precautions: *The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.*

Adverse Reactions: *Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.*

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

BRS-DZ-L42

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Comparison of Adverse Effects for CAPOTEN (≤ 100 mg) versus Placebo in Hypertensive Patients with Normal Renal Function (N = 1,622)‡[2]

ADVERSE EFFECT	CAPOTEN (N = 1,174) (% affected)	Placebo (N = 448) (% affected)
Headache	5.2	6.9
Rash	3.7	2.5
Dizziness	3.5	2.0
Nausea	3.2	2.0
Fatigue	3.1	2.0
Taste alteration	1.5	1.1
Gastrointestinal	1.4	0.7
Diarrhea	1.1	1.1

‡None of the differences between captopril and placebo was statistically significant. For the most part, adverse effects were mild and transient and usually did not require discontinuation of therapy. Only 5.5% of the patients in this data base discontinued because of an adverse effect. Data include adverse effects for CAPOTEN with an incidence greater than 1%.

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INDICATIONS: Hypertension – CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia ($<1000/mm^3$) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine <1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count $<1000/mm^3$) withdraw captopril and closely follow the patient's course.

Proteinuria – Total urinary proteins >1 g/day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy, patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension – Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in mean blood pressure $>20\%$ were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function,* Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine $>20\%$ above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction.

Surgery/Anesthesia – If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C – There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic – Neutropenia/agranulocytosis have occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients – reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur, see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia – About 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg also available in bottles of 1000), and in UNIMATIC® single dose packs of 100 tablets. (J3-658D)

References:

1. PDS Alpha, *National Prescription Report,* Pharmaceutical Data Services, Subsidiary of McKesson Corporation.
2. Data on file, Squibb Institute for Medical Research.

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

January 22-25—**Treatment Options in End Stage Cardiac Disease.** Loews Ventana Canyon Resort, Tucson. Thursday-Sunday. Contact: U of A.

February 2-7—**Emergency Care Update IX.** Monday-Saturday. Contact: U of A.

February 12-15—**Arizona Academy of Family Physicians Scientific Assembly—1987.** Scottsdale Hilton, Scottsdale. Thursday-Sunday. Contact AAFP, (602) 249-2021.

Feburary 13-15—**Anesthesia for the 80s.** La Paloma Resort, Tucson. Friday-Sunday. Contact: Beverly Richter for Arizona Society of Anesthesiologists, (602) 246-8901.

February 18-21—**Crises and Controversies in Pediatrics.** Doubletree Inn, Tucson. Wednesday-Saturday. Contact: U of A.

February 19—**First Annual Interventional Angiography Symposium.** Thursday. Contact: Christine Campbell for St Luke's Medical Center, (602) 947-7756.

February 19-21—**Frontiers in Ophthalmology.** Thursday-Saturday. Contact: Christine Campbell for St Luke's Medical Center, (602) 947-7756.

February 22-25—**First Annual Barrow Neurological Institute Magnetic Resonance Imaging Conference.** Mountain Shadows Resort, Scottsdale. Sunday-Wednesday. Contact: Barrow Neurological Institute, (602) 285-3178 or (800) BARROW1.

February 25-27—**Tenth Annual Mid-Winter Symposium in OB/GYN.** Scottsdale Hilton, Scottsdale. Wednesday-Friday. Contact: Maricopa Medical Center, (602) 267-5444.

February 26-28—**Neurology and Neurosurgery of the Aging.** Mountain Shadows Resort, Scottsdale. Thursday-Saturday. Contact: Barrow Neurological Institute, (602) 285-3178 or (800) BARROW1.

March 4-8—**11th Annual Valley of the Sun Dermatologic Symposium.** Loews Paradise Valley Resort, Scottsdale. Wednesday-Sunday. Contact: Millard Thaler, MD, 2055 E Southern, #B, Tempe 85282.

March 11-13—**Them Ol' Bones.** Wednesday-Friday. Contact: Christine Campbell for St Luke's Medical Center, (602) 947-7756.

March 17-20—**Pediatric Update—1987.** La Posada Resort, Scottsdale. Tuesday-Friday. Contact: Phoenix Children's Hospital, (602) 239-4350.

March 19-21—**23rd Annual Arizona Chest Symposium.** Doubletree Hotel, Tucson. Thursday-Saturday. Contact: Sandy Younker-Hellman, RN, U of A, (602) 327-5461.

March 21-22—**13th Annual James H. McDonald Urological Seminar.** Sheraton Scottsdale Resort, Scottsdale. Saturday-Sunday. Contact: Maricopa Medical Center, (602) 267-5371.

April 6-8—**Practical Cardiology for the Family Physician.** La Posada Resort, Scottsdale. Monday-Wednesday. Contact: American College of Cardiology, (301) 897-5400, ext 226.

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This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

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For more information, call your local ACS Unit or write to the American Cancer Society, 4 West 35th Street, New York, NY 10001.

ALLERGY

December 21-27—**Allergy, Immunology and the Practicing Physician—"Christmas '86—Maui."** Hawaii Medical Association at Royal Lahaina Resort, Kaanapali Beach, Maui. One week. 18 hrs. Fee: $385. Contact: Joe Harrison, MD, Symposium Maui, Inc, PO Box 10185, Lahaina, HI 96761. (808) 879-8182 or 661-8032.

February 11-14—**Immunology and the Clinical Practice of Allergy.** UCSD at San Diego Hilton Beach and Tennis Resort. Wednesday-Saturday. 20 hrs. Contact: UCSD

ANESTHESIOLOGY

January 8-11—**Anesthesia Update—1987.** UCSD at Hotel Inter-Continental, San Diego. Thursday-Sunday. 20 hrs. Contact: UCSD.

January 30—February 1—**25th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesi-

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

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Efficiency Plus *415/348-0539*
Express Insurance Claims Service, Inc. *619/322-5124*
M/D Systems, Inc. *800/272-3285 - 818/995-7111*
Medical Computer Billing, Inc. *916/969-1000*
Medical Concepts Billing Service *714/351-0115*
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Medicom Corporation *415/956-0382*
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The Limhi Corporation *714/652-5112*
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Lab Force *214/349-4025*
M/D Systems, Inc. *800/272-3285 -- 818/995-7111*
MDR Systems, Inc. *415/349-0810*
Management Consulting Company *916/444-9370*
Medical Systematics, Inc. *209/723-6655*
Orion Systems *408/727-9900*
PSC Software, Inc. *415/786-9722*
RX Computers, Inc. *415/893-6226*
Sierra Medical Systems *800/874-5400 -- 916/361-2165*

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This advertisement is paid for in part by the organizations listed above and comprises a partial list of businesses approved to submit Medicare Part B claims to Blue Shield of California Medicare. ECS/EZ does not endorse any particular system, and encourages providers to research and select the system that is best for their particular business needs.

(Continued from Page 752)

ology Foundation at Marriott Hotel, Los Angeles. Friday-Sunday. 15 hrs. Fee: $175. Contact: Wayne Herbert, MD, Children's Hospital of Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

February 8-12—**15th Obstetric Anesthesia Conference.** Ohio State University Hospital at Sheraton Waikiki Hotel, Hawaii. Sunday-Thursday. Contact: Ohio State University Hospital, Dept of Anesthesiology, 410 W 10th Ave, Columbus, OH 43210. (614) 421-8487.

March 20-22—**Obstetrical Anesthesia—1987.** UCSF at Hotel Meridien, San Francisco. Friday-Sunday. Contact: UCSF.

March 21-22—**Los Angeles County Society of Anesthesiologists 32nd Postgraduate Assembly.** Los Angeles Hilton Hotel. Saturday-Sunday. Contact: LA County Society of Anesthesiologists, 333 S Beverly Dr, Ste 111, Beverly Hills 90212. (213) 556-8865.

April 27-May 1—**California Society of Anesthesiologists Hawaiian Seminar.** Sheraton Kauai Hotel, Poipu Beach, Hawaii. Monday-Friday. 20 hrs. Contact: Linda P. Londerville, CSA, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

CANCER

February 16-18—**Clinical Hematology and Oncology—1987.** Scripps Clinic, La Jolla at Vacation Village Resort, San Diego. Monday-Wednesday. Contact: Bonny Mower, Dept of Academic Affairs, Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

March 7—**Supportive Care of the Cancer Patient.** UCI at Long Beach. Saturday. 6 hrs. Contact: UCI.

March 12-14—**2nd International Conference on Monoclonal Antibody Immunoconjugates for Cancer.** UCSD at Hotel Inter-Continental, San Diego. Thursday-Saturday. Contact: UCSD.

March 18-20—**7th Annual Current Approaches to Radiation Oncology, Biology and Physics.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday. 18 hrs. Fee: $275-325. Contact: UCSF

April 3—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Friday. 7 hrs. Fee: $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

April 5—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Newporter Hotel, Newport Beach. Sunday. Fee: $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

May 1—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Vacation Village Resort, San Diego. Friday. Fee: $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

May 3—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sunday. Fee: $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

CARDIOLOGY

January 23-25—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

January 29-31—**Cardiology '87.** Scripps Memorial Hospital, La Jolla at La Jolla Marriott Hotel, San Diego. Thursday-Saturday. 18 hrs. Fee: $275. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 29-31—**Clinical Nuclear Cardiology: Case Review with the Experts.** American College of Cardiology at Cedars-Sinai Medical Center, Los Angeles. Thursday-Saturday. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400.

February 4-7—**4th Annual Cardiopulmonary Conference.** American College of Chest Physicians at Lake Tahoe. Wednesday-Saturday. Contact: ACCP, 911 Busse Highway, Park Ridge, IL 60068. (312) 698-2200 or (916) 739-8833.

February 5-8—**Pathophysiology and Techniques of Cardiopulmonary Bypass: VII.** Cardiothoracic Research and Education Foundation at Sheraton Island East Hotel, San Diego. Thursday-Sunday. 15 hrs. Fee: $300. Contact: CREF, PO Box 33185, San Diego 92103. (619) 692-9115.

February 6-7—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Bally's (MGM) Grand Hotel, Las Vegas, Nevada. Friday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

February 9-13—**2nd Annual Cardiovascular Conference.** American College of Cardiology at Sheraton Royal Waikaloa Hotel, Kona Coast, Hawaii. Mon-

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- Certain subjective symptoms such as malaise and drowsiness, which may interfere with physical or mental activity, have not been characteristic of VASOTEC. This may be related to the specificity of action of VASOTEC on the renin-angiotensin-aldosterone system.

- In worldwide controlled clinical trials, VASOTEC was generally well tolerated. The overall percentage of patients reporting adverse effects was comparable to placebo.

- For the most part, adverse effects in clinical trials were mild and transient and usually did not require discontinuation of therapy.

Angioedema has been reported in patients treated with angiotensin-converting-enzyme inhibitors, including VASOTEC (0.2% of patients treated with VASOTEC). Angioedema associated with laryngeal edema and/or shock may be fatal. **If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately** (see ADVERSE REACTIONS).

Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. Therefore, discontinue therapy with a beta blocker only in accordance with the recommendations in the prescribing information for that product. Begin therapy with VASOTEC on the day following the last day of therapy with the beta blocker.

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Contraindications: VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product.

Warnings: *Angioedema* Angioedema has been reported in patients treated with angiotensin-converting-enzyme inhibitors, including VASOTEC. Angioedema associated with laryngeal edema and/or shock may be fatal. **If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased.

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Neutropenia/Agranulocytosis: Another angiotensin-converting-enzyme inhibitor has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General. Impaired Renal Function:* In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of VASOTEC and/or discontinuation of the diuretic may be required.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia. (See *Drug Interactions*.)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, tongue, difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC® (Enalapril Maleate, MSD) is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC may attenuate potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril, but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

There are no adequate and well-controlled studies in pregnant women. VASOTEC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2677 patients.

The most frequent clinical adverse experiences in controlled trials were: headache (4.8%), dizziness (4.6%), and fatigue (2.8%). For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences was not related to total daily dosage within the range of 10 to 40 mg. The overall percentage of patients treated with VASOTEC reporting adverse experiences was comparable to placebo.

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.6%), rash (1.5%), hypotension (1.4%), cough (1.3%), nausea (1.3%), and orthostatic effects (1.3%).

Clinical adverse experiences occurring in 0.5% to 1.0% of patients in the controlled trials included:

Cardiovascular: Syncope, orthostatic hypotension, palpitations, chest pain.

Nervous System: Insomnia, nervousness, paresthesia, somnolence.

Gastrointestinal System: Abdominal pain, vomiting, dyspepsia.

Other: Dyspnea, muscle cramps, hyperhydrosis, impotence, pruritus, asthenia.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema and/or shock may be fatal. If angioedema of the face, tongue, or glottis occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: Combining the results of clinical trials in patients with hypertension or congestive heart failure, hypotension (including postural hypotension and other orthostatic effects) was reported in 2.3% of patients following the initial dose of enalapril or during extended therapy. In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. (See WARNINGS.)

Clinical Laboratory Test Findings:

Hyperkalemia: (See PRECAUTIONS.)

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.)

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in hypertensive patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

In overseas marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

For more detailed information, consult your MSD representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486. J6VS11(003)

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day-Friday. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 227.

February 13-14—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Americana Resort Hotel, Palm Springs. Friday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

March 22-25—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Royal Lahaina Hotel, Maui, Hawaii. Sunday-Wednesday. 13 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

March 27-28—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Desert Inn Hotel, Las Vegas, Nevada. Friday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

April 10-11—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Inter-Continental Hotel, San Diego. Friday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

April 27-May 6—**Cardiology for the Consultant.** Scripps Clinic and Research Foundation at Rancho Santa Fe Inn, Rancho Santa Fe. Monday-Wednesday. 40 hrs. Fee: $800. Contact: Bonny Mower, Dept of Academic Affairs, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

May 1-2—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Hotel Inter-Continental, San Diego. Friday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or in CO 798-9682.

DERMATOLOGY

January 23-25—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** Continuing Medical Education Associates, San Diego. Friday-Sunday. 20 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

EMERGENCY MEDICINE

January 12-16—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD at San Diego Hilton Hotel. Monday-Friday. 32 hrs. Fee: $325-440. Contact: UCSD.

February 2-4—**Trauma Management—1987.** UCSD at Hotel Inter-Continental, San Diego. Monday-Wednesday. 20 hrs. Contact: UCSD.

February 22-27—**10th Annual UCD Winter Conference: Emergency Medicine—1987.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sunday-Friday. 27 hrs. Fee: $395. Contact: UCD.

February 28—**Major and Minor Hand Problems in the Emergency Department.** UCSF at UCSF. Saturday. 7 hrs. Contact: UCSF.

March 8-13—**8th Annual Mammoth Mountain Emergency Medicine Ski Conference.** UCI at Mammoth Lakes. Sunday-Friday. 20 hrs. Fee: $350. Contact: Medical Conferences, Inc, PO Box 52-B, Newport Beach 92662. (714) 650-4156.

March 16-20—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium II and Advanced Emergency Procedures Laboratory.** UCSD. Monday-Friday. 32 hrs. Fee: $325-440. Contact: UCSD.

April 11-18—**Infectious and Toxicologic Emergencies.** Scripps Memorial Hospital, Encinitas at Waiohai Resort and Poipu Beach Hotel, Kauai, HI. One week. 21 hrs. Fee: $375. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

April 25-May 1—**Critical Care Medicine.** University of Colorado at Inter-Continental Hotel, Maui, Hawaii. Saturday-Friday. 20 hrs. Fee: $395. Contact: Univ of CO, Office of CME, 4200 E 9th Ave, Box C-295, Denver, CO 80262. (303) 394-5195.

May 4-8—**Postgraduate Institute for Emergency and Primary Care Physicians—Symposium I and Advanced Emergency Procedures Laboratory.** UCSD at Hotel Inter-Continental, San Diego. Monday-Friday. 32 hrs. Fee: $325-440. Contact: UCSD.

May 13-17—**9th Annual: Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wednesday-Sunday. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

INTERNAL MEDICINE

December 27-January 1—**Advances in Internal Medicine.** University of Washington at Kauai Sheraton, Kauai. Saturday-Thursday. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle 98195. (206) 543-1050.

January 14—**Urology Update.** LLU at LLU. Wednesday. 4 hrs. Fee: $60. Contact: LLU.

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JOHN A. STARKWEATHER, PhD

From the Department of Psychiatry and Langley Porter Psychiatric Institute, University of California, San Francisco, School of Medicine.

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FREDERICK R. JELOVSEK, MD

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PHIL R. MANNING, MD

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914 **Classified Advertising**

924 **Western State Medical Associations' Meetings**

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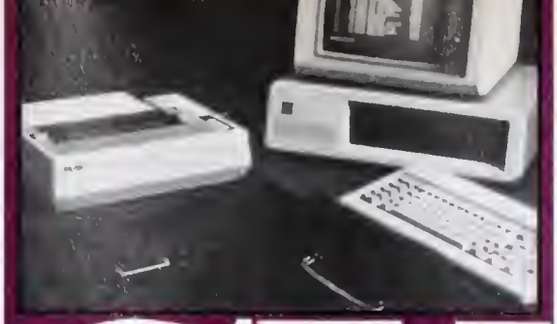

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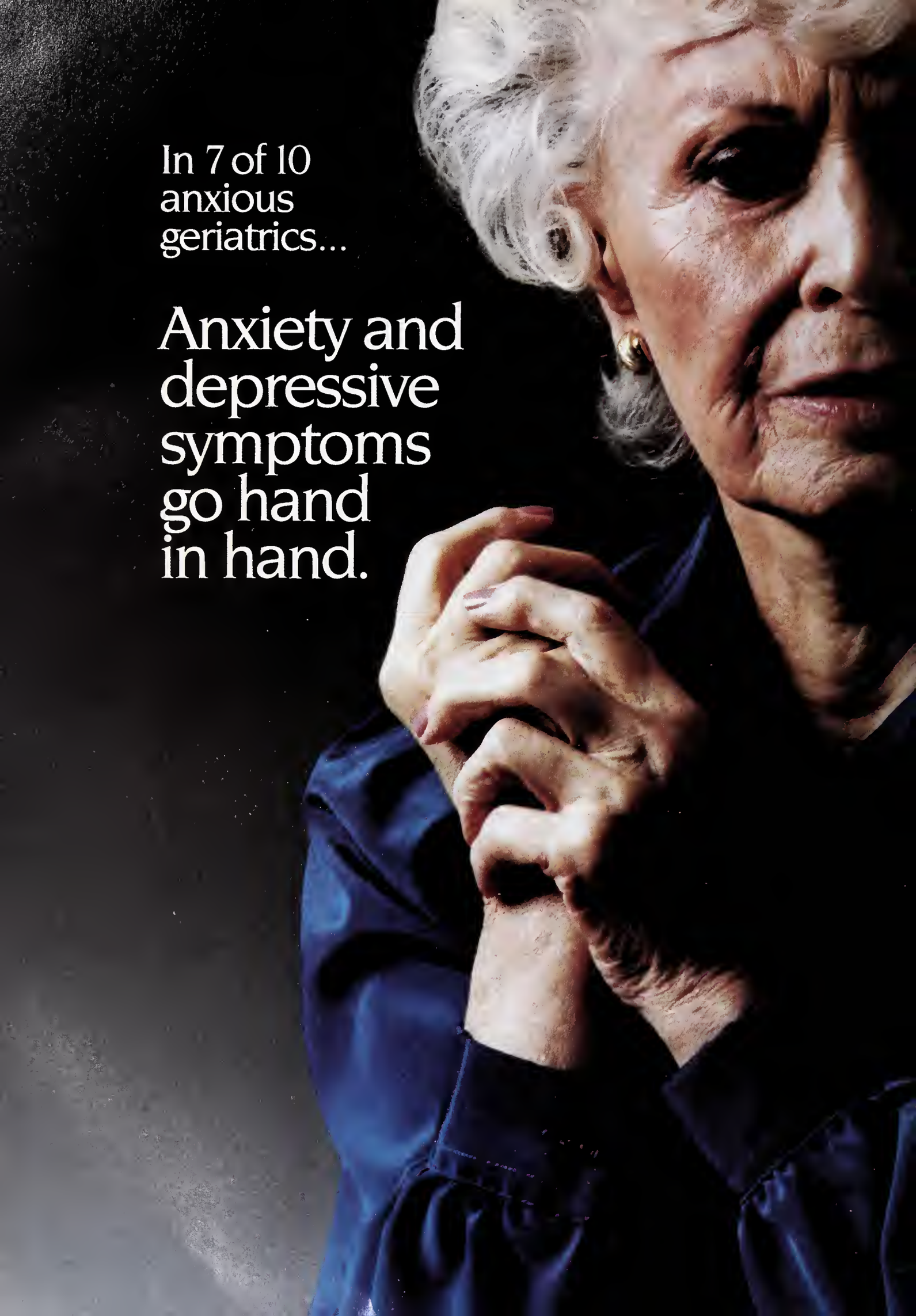
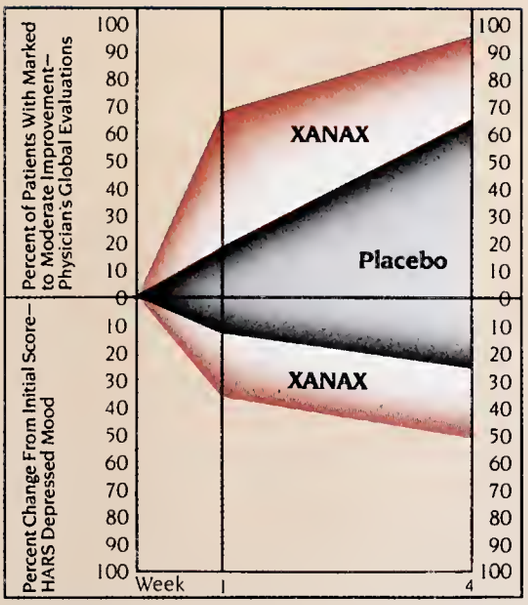

In 7 of 10
anxious
geriatrics...
Anxiety and
depressive
symptoms
go hand
in hand.

Xanax effectively relieves anxiety with associated depressive symptoms.



In a recent clinical study[1] of 83 geriatric patients with clinical anxiety, 73% were diagnosed as having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than does placebo in reducing the Hamilton Anxiety Rating Scale Total Score and individual items, including depressed mood (see Figure).

With clinical advantages for geriatric patients.

- Effectively relieves the symptoms of anxiety
- Also relieves anxiety with associated depressed mood
- Well tolerated—side effects, if they occur, are generally observed at the beginning of therapy and usually disappear with continued medication. Drowsiness and light-headedness were the most commonly reported adverse reactions
- Does not cause cardiovascular toxicity
- **Specific geriatric dosage**—0.25 mg, two or three times daily

1. Cohn JB: Double-blind safety and efficacy comparison of alprazolam and placebo in the treatment of anxiety in geriatric patients. *Curr Ther Res* 1984;35(1):100-112.

Xanax® 0.25 mg Tablets

alprazolam C IV

Upjohn 100 A Century of Caring 1886·1986

© 1986 The Upjohn Company
Kalamazoo, Michigan 49001, USA

Please see adjacent page for brief summary of prescribing information.

XANAX® Tablets
(alprazolam) ℞

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests*: Not ordinarily required in otherwise healthy patients. *Drug Interactions*: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions*: No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility*: No carcinogenic potential or impairment of fertility in rats. *Pregnancy*: See Warnings. *Nonteratogenic Effects*: The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery*: No established use. *Nursing Mothers*: Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use*: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, eg, drowsiness or lightheadedness.

Central nervous system. Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes of unknown significance have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class*: XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

B-4-S

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I-5963
January 1986

vicodin® C III

hydrocodone bitartrate 5 mg (Warning: May be habit forming.) with acetaminophen 500 mg

INDICATIONS AND USAGE: For the relief of moderate to moderately severe pain.
CONTRAINDICATIONS: Hypersensitivity to acetaminophen or hydrocodone.
WARNINGS
Drug Abuse and Dependence: VICODIN is subject to the Federal Controlled Substances Act (Schedule III). Psychic dependence, physical dependence and tolerance may develop upon repeated administration of narcotics; therefore, VICODIN should be prescribed and administered with the same caution appropriate to the use of other oral-narcotic-containing medications.
Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on brain stem respiratory centers. Hydrocodone also affects centers that control respiratory rhythm, and may produce irregular and periodic breathing.
Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.
Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.
PRECAUTIONS
Special Risk Patients: VICODIN should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture.
Information For Patients: VICODIN, like all narcotics, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.
Cough Reflex: Hydrocodone suppresses the cough reflex; caution should be exercised when VICODIN is used postoperatively and in patients with pulmonary disease.
Drug Interactions: The CNS-depressant effects of VICODIN may be additive with that of other CNS depressants. When combined therapy is contemplated, the dose of one or both agents should be reduced. The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone. The concurrent use of anticholinergics with hydrocodone may produce paralytic ileus.
Usage in Pregnancy: Pregnancy Category C. Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the human dose. There are no adequate and well-controlled studies in pregnant women. VICODIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose.
Labor and Delivery: Administration of VICODIN to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.
Nursing Mothers: It is not known whether this drug is excreted in human milk; therefore, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS
Central Nervous System: Sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, dizziness, psychic dependence, mood changes.
Gastrointestinal System: Nausea and vomiting may occur; they are more frequent in ambulatory than in recumbent patients. Prolonged administration of VICODIN may produce constipation.
Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported.
Respiratory Depression: (See WARNINGS.)
DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. However, tolerance to hydrocodone can develop with continued use, and the incidence of untoward effects is dose related.
The usual dose is one tablet every six hours as needed for pain (if necessary, this dose may be repeated at four-hour intervals.) In cases of more severe pain, two tablets every six hours (up to eight tablets in 24 hours) may be required.
Revised, April 1982. 5685

KNOLL PHARMACEUTICAL COMPANY
30 NORTH JEFFERSON ROAD, WHIPPANY, NEW JERSEY 07981

Knoll Pharmaceuticals
A Unit of BASF K&F Corporation
Whippany, New Jersey 07981

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AN OPEN LETTER TO CALIFORNIA PHYSICIANS

Vicodin® is a Schedule III analgesic in California

Dear Doctor,

As a Schedule III drug, prescriptions for Vicodin may be:

- Refilled 5 times within 6 months.
- Telephoned into local pharmacies.
- Written on regular prescription pads. No triplicate pads are necessary.

We regret any inconvenience caused by the inadvertent reclassification of Vicodin in California to a Schedule II status during July and August of this year. This has been rectified by the California assembly.

Vicodin will continue to be sampled per your request. Thank you for your support of Vicodin.

Please continue to specify "Dispense as written" for the original hydrocodone analgesic.

Sincerely,

John La Lota

John La Lota
Product Manager
Vicodin

vicodin® III

Hydrocodone bitartrate 5 mg. (Warning: May be habit forming)
with acetaminophen 500 mg.

Greater patient acceptance and longer lasting pain relief.

Please see accompanying brief summary.

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5779/9-86

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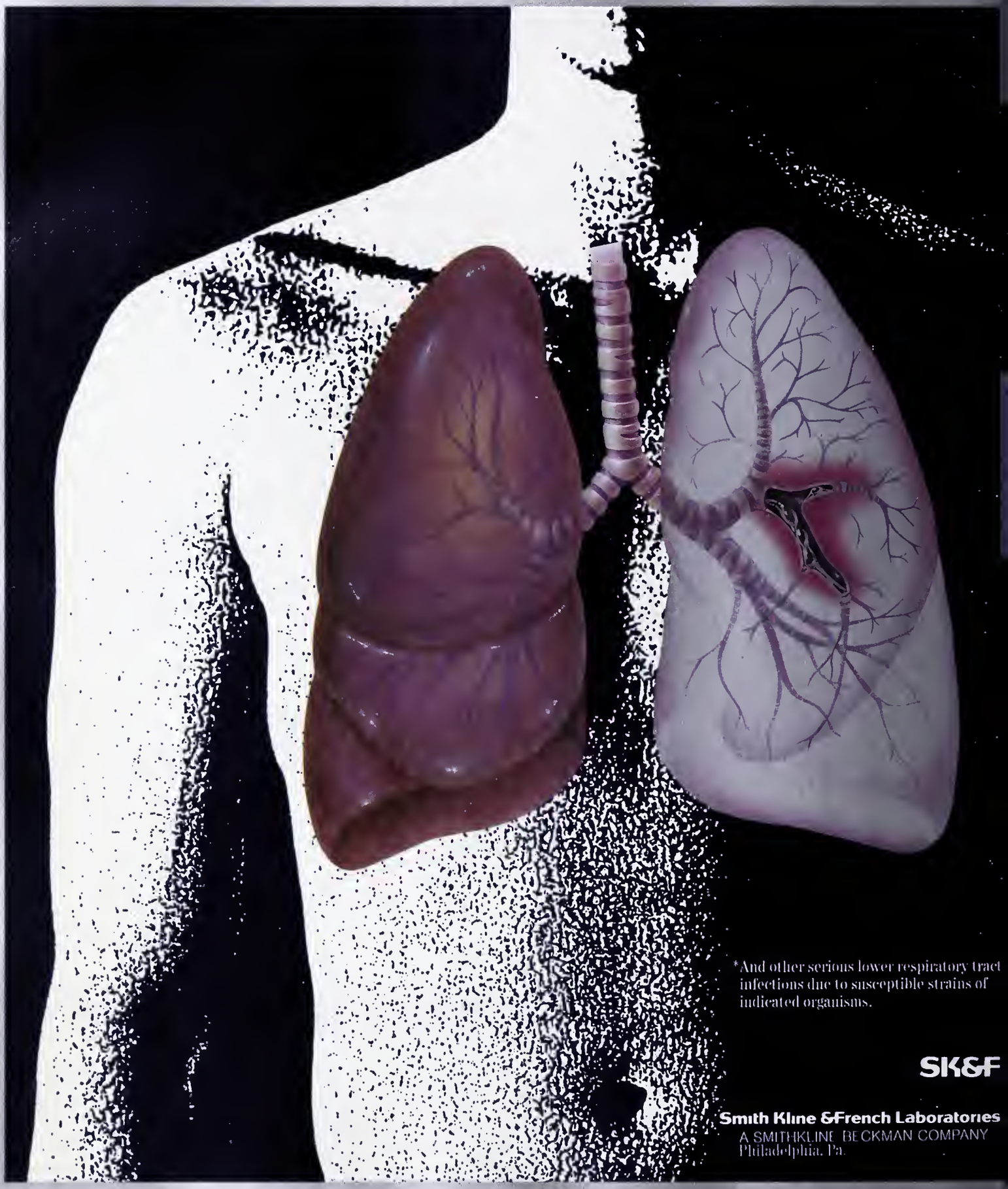
In Pneumonia*... The



*And other serious lower respiratory tract infections due to susceptible strains of indicated organisms.

SK&F

Smith Kline &French Laboratories
A SMITHKLINE BECKMAN COMPANY
Philadelphia, Pa.

'Monocid' Advantage

The Benefits of Once-Daily Dosing

- 24-Hour Coverage of Common Pathogens
- Effective Against Ampicillin-Resistant *H. influenzae*
- I.V. or I.M.: Hospital or Outpatient Management
- Lowest Cost per Course of Therapy[1-4]

Plus The Efficacy You Expect

- 95% Clinical Success (91% cured,* 4% improved) with Once-Daily Dosing[5-7]

Once-a-Day/Broad-Spectrum

MONOCID®

IV/IM

brand of sterile

cefonicid sodium

(lyophilized)

*Since the definition of "cure" may vary significantly among clinical settings and investigators, the reader is urged to consult the references cited.

Before prescribing, please consult the brief summary of 'Monocid' prescribing information on the following page.

Once-a-Day Therapy in

PNEUMONIA

MONOCID®

IV/IM brand of sterile

cefonicid sodium

(lyophilized)

The 'Monocid' Advantage
The Benefits of Once-Daily Dosing
Plus the Efficacy You Expect

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

INDICATIONS AND USAGE

Monocid (sterile cefonicid sodium, SK&F) is indicated in the treatment of infections due to susceptible strains of the microorganisms listed below:

LOWER RESPIRATORY TRACT INFECTIONS, due to *Streptacoccus pneumoniae* (formerly *D. pneumoniae*); *Klebsiella pneumaniae*; *Escherichia coli*; and *Hemophilus influenzae* (ampicillin-resistant and ampicillin-sensitive).

URINARY TRACT INFECTIONS, due to *Escherichia coli*; *Proteus mirabilis* (indole-negative *Proteus*); and *Klebsiella pneumoniae*.

SKIN AND SKIN STRUCTURE INFECTIONS, due to *Staphylococcus aureus* and *S. epidermidis*; *Streptacoccus pyogenes* (Group A *Streptococcus*) and *S. agalactiae* (Group B *Streptacaccus*).

SEPTICEMIA, due to *Streptacaccus pneumoniae* (formerly *D. pneumaniae*) and *Escherichia coli*.

BONE AND JOINT INFECTIONS, due to *Staphylococcus aureus*.

Therapy with 'Monocid' may be initiated pending results of susceptibility studies. Treatment should be adjusted according to findings.

SURGICAL PROPHYLAXIS

Administration of a single 1 gram dose of 'Monocid' before surgery may reduce the incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (e.g., colorectal surgery, vaginal hysterectomy, or cholecystectomy in high-risk patients), or in patients in whom infection at the operative site would present a serious risk (e.g., prosthetic arthroplasty, open heart surgery). Although cefonicid has been shown to be as effective as cefazolin in prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery or prosthetic heart valve replacement.

In cesarean section, the use of 'Monocid' (after the umbilical cord has been clamped) may reduce the incidence of certain postoperative infections.

When administered one hour prior to surgical procedures for which it is indicated, a single 1 gram dose of 'Monocid' provides protection from most infections due to susceptible organisms throughout the course of the procedure and for approximately 24 hours after administration. Intraoperative and postoperative administration of 'Monocid' is not necessary. Daily doses of 'Monocid' may be administered for two additional days in patients undergoing prosthetic arthroplasty or open heart surgery.

Before using 'Monocid' concomitantly with other antibiotics, the prescribing information for those agents should be reviewed for contraindications, warnings, precautions and adverse reactions. Renal function should be carefully monitored.

CONTRAINDICATIONS

'Monocid' is contraindicated in persons who have shown hypersensitivity to cephalosporin antibiotics.

WARNINGS

BEFORE THERAPY WITH 'MONOCID' IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider that diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics alters normal flora of the colon and may permit overgrowth of Clostridia. Studies indicate a toxin produced by *Clastridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance and when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should also be considered.

PRECAUTIONS

General: With any antibiotic, prolonged use may result in overgrowth of nonsusceptible organisms. Careful observation is essential, and appropriate measures should be taken if superinfection occurs.

Drug Interactions: Nephrotoxicity has been reported following concomitant administration of other cephalosporins and aminoglycosides.

Pregnancy: (Category B.) Reproduction studies have been performed in mice, rabbits and rats at doses up to an equivalent of 40 times the usual adult human dose and have revealed no evidence of impaired fertility or harm to the fetus due to 'Monocid'. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.

Labor and Delivery: In cesarean section, 'Monocid' should be administered only after the umbilical cord has been clamped.

Nursing Mothers: 'Monocid' is excreted in human milk in low concentrations. Caution should be exercised when 'Monocid' is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

Beta-lactam antibiotics with methyl-thio-tetrazole side chains have been shown to cause testicular atrophy in prepubertal rats, which persisted into adulthood and resulted in decreased spermatogenesis and decreased fertility. Cefonicid, which contains a methylsulfonic-thio-tetrazole moiety, has no adverse effect on the male reproductive system of prepubertal, juvenile or adult rats when given under identical conditions.

ADVERSE REACTIONS

'Monocid' is generally well tolerated and adverse reactions have occurred infrequently. The most common adverse reaction has been pain on I.M. injection. On-therapy conditions occurring in greater than 1% of 'Monocid'-treated patients were:

Injectian Site Phenamena (5.7%): Pain and/or discomfort on injection; less often, burning, phlebitis at I.V. site.

Increased Platelets (1.7%).

Increased Eosinophils (2.9%).

Liver Function Test Alteratians (1.6%): Increased alkaline phosphatase, increased SGOT, increased SGPT, increased GGTP, increased LDH.

Less frequent on-therapy conditions occurring in less than 1% of 'Monocid'-treated patients were:

Hypersensitivity Reactions: Fever, rash, pruritus, erythema, myalgia and anaphylactoid-type reactions have been reported.

Hematalogy: Decreased WBC, neutropenia, thrombocytopenia, positive Coombs' test.

Diarrhea.

DOSAGE AND ADMINISTRATION

General

The usual adult dosage is 1 gram of 'Monocid' given once every 24 hours, intravenously or by deep intramuscular injection. Doses in excess of 1 gram daily are rarely necessary; however, in exceptional cases dosage of up to 2 grams given once daily have been well tolerated. When administering 2 gram I.M. doses once daily, one-half the dose should be administered in different large muscle masses.

Surgical Prophylaxis

When administered one hour prior to appropriate surgical procedures (see Indications and Usage), a 1 gram dose of 'Monocid' provides protection from most infections due to susceptible organisms throughout the course of the procedure and for approximately 24 hours after administration. Intraoperative and postoperative administration of 'Monocid' is not necessary. Daily doses of 'Monocid' may be administered for two additional days in patients undergoing prosthetic arthroplasty or open heart surgery.

In cesarean section 'Monocid' should be administered only after the umbilical cord has been clamped.

General Guidelines for Dosage of 'Monocid', I.V. or I.M.

Type of Infection	Daily Dose (grams)	Frequency
Uncomplicated Urinary Tract	0.5	once every 24 hours
Mild to Moderate	1	once every 24 hours
Severe or Life-Threatening	2*	once every 24 hours
Surgical Prophylaxis	1	1 hour preoperatively

*When administering 2 gram I.M. doses once daily, one-half the dose should be administered in different large muscle masses.

Impaired Renal Function

Modification of 'Monocid' dosage is necessary in patients with impaired renal function. Before prescribing, consult Dosage and Administration section of complete prescribing information.

HOW SUPPLIED

'Monocid' is supplied in vials equivalent to 500 mg. and 1 gram of cefonicid; in "Piggyback" Vials for I.V. admixture equivalent to 1 gram of cefonicid; and in Pharmacy Bulk Vials equivalent to 10 grams of cefonicid.

BRS-MC:L15 Date of issuance Feb. 1986

References:

1. Report from International Health Services, Ltd., Jan.-Mar., 1986.
2. Report from Health Information Programs, Inc., Jan.-June, 1985.
3. Smeeding, J.E.: Cost Analysis of Second-Generation Cephalosporins and Economic Implications of Decreased Frequency of Administration, *Adv Ther.* 2:260-267 (Sept.-Oct.) 1985.
4. Correspondence from Tom C. Snader Consultants, Inc., April 1986.
5. Geckler, R.W., et al.: *Rev. Infect. Dis.* 6:S847-S852, (Nov.-Dec.) 1984.
6. Wallace, R.J., Jr., et al.: *Antimicrob. Agents Chemother.* 21:231-235 (Feb.) 1982.
7. Simelaro, J.P., et al.: *Adv. Ther.* 2:192-202 (Sept.-Oct.) 1985.

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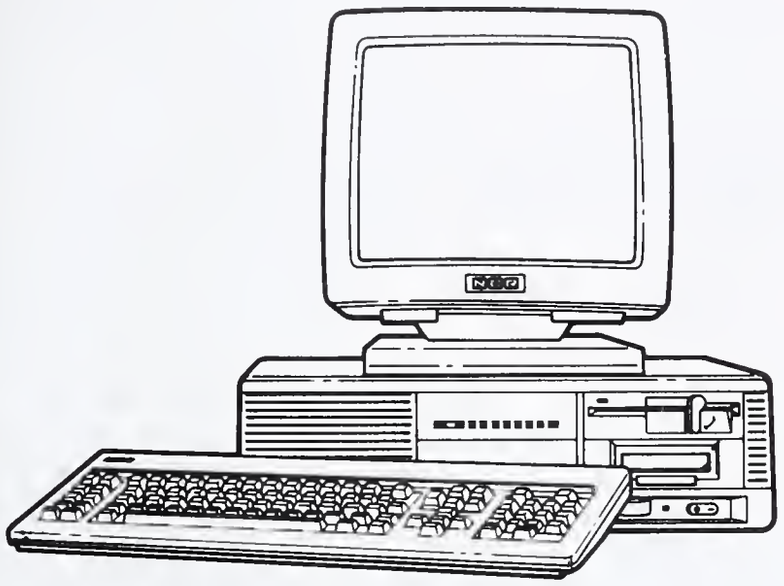

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(Continued from Page 759)

January 30-31—**Update on Uses of Lasers in Urology.** UCI at Long Beach. Friday-Saturday. Contact: UCI.

January 31-February 7—**Infectious Disease in General Medical and Pediatric Practice.** University of Colorado at Inter-Continental Hotel, Maui, Hawaii. One week. 24 hrs. Fee: $395. Contact: Univ of CO, Office of CME, 4200 E 9th Ave, Box C-295, Denver, CO 80262. (303) 394-5195.

February 1-5—**Internal Medicine 1987: An Office Practice Review.** Sharp Memorial Hospital at Hotel Del Coronado, San Diego. Sunday-Thursday. 28 hrs. Fee: $395. Jackie Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

February 1-6—**Winter Urologic Forum.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sunday-Friday. 22 hrs. Fee: $370. Contact: UCD.

February 4-6—**Emerging Technology and Future Trends in Clinical Laboratory Molecular Analyses.** Scripps Clinic and Research Foundation at Vacation Village Resort, San Diego. Wednesday-Friday. 20 hrs. Contact: Bonny Mower, Dept of Academic Affairs, Scripps Clinic and Research Foundation, Box 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

February 8-13—**General Internal Medicine: Concepts and Controversies.** UCSF at Hyatt Lake Tahoe, Nevada. Sunday-Friday. Contact: UCSF

February 11-13—**20th Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday. 15 hrs. Contact: UCSF.

February 13-14—**5th Annual Infectious Disease.** UCD at Sacramento. Friday-Saturday. Contact: UCD.

February 19-21—**Advances in the Management of Infectious Disease.** University of Michigan at Kahala Hilton Hotel, Honolulu, Hawaii. Thursday-Saturday. 11.75 hrs. Fee: $285. Contact: Gayle Fox, Office of CME, Univ of Michigan, Towsley Center, Box 0201, Ann Arbor, Michigan 48109-0201. (313) 763-1400.

March 7-14—**Topics in Internal Medicine for Primary Care Physicians.** University of Colorado at Molokai Sheraton, Molokai, Hawaii. One week. 20 hrs. Fee: $395. Contact: Univ of CO, Office of CME, 4200 E 9th Ave, Box C-295, Denver, CO 80262. (303) 394-5195.

March 11—**Rheumatology: Osteoarthritis and Nonsteroidal Drugs.** LLU. Wednesday. 4 hrs. Fee: $60. Contact: LLU.

March 30-April 1—**Federation of Western Societies of Neurological Science 24th Annual Meeting.** Monday-Wednesday at Hotel Del Coronado, Coronado. Contact: Patrick D. Lyden, MD, Dept of Neurosciences, UCSD Medical Center H-815A, 225 W Dickinson St, San Diego 92103. (619) 452-3940.

April 8-10—**Advances in Infectious Disease.** UCSF at Hyatt Regency Embarcadero, San Francisco. Wednesday-Friday. 16 hrs. Fee: $350.

April 23-24—**7th Annual Infectious Diseases—Clinical Update.** Sutter Community Hospitals and Mercy Hospital of Sacramento at Red Lion Inn, Sacramento. Thursday-Friday. 14 hrs. Contact: Infectious Diseases Symposium, Metro Centre, 1600 Sacramento Inn Way, Ste 132, Sacramento 95815. (916) 925-1366.

May 2—**New Treatments in Liver and Biliary Tract Disease.** Scripps Clinic and Research Foundation, La Jolla. Saturday. 7 hrs. Fee: $110. Contact: Bonny Mower, Dept of Academic Affairs, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

May 18-22—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday. 32 hrs. Fee: $440. Contact: UCSF.

OB/GYN

January 12-16—**OB/GYN Review II.** USC at Pasadena Hilton Hotel. Monday-Friday. 35.75 hrs. Fee: $545. Contact: USC.

January 14-17—**GYN Review.** USC at Pasadena Hilton Hotel. Wednesday-Saturday. 28.5 hrs. Fee: $430. Contact: USC.

January 16-18—**Gynecology Update for the Primary Care Physician.** UCSD at Vacation Village Resort, San Diego. Friday-Sunday. 15 hrs. Fee: $275. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 17—**OB/GYN Pathology II.** USC at Pasadena Hilton Hotel. Saturday. 6.25 hrs. Fee: $105. Contact: USC.

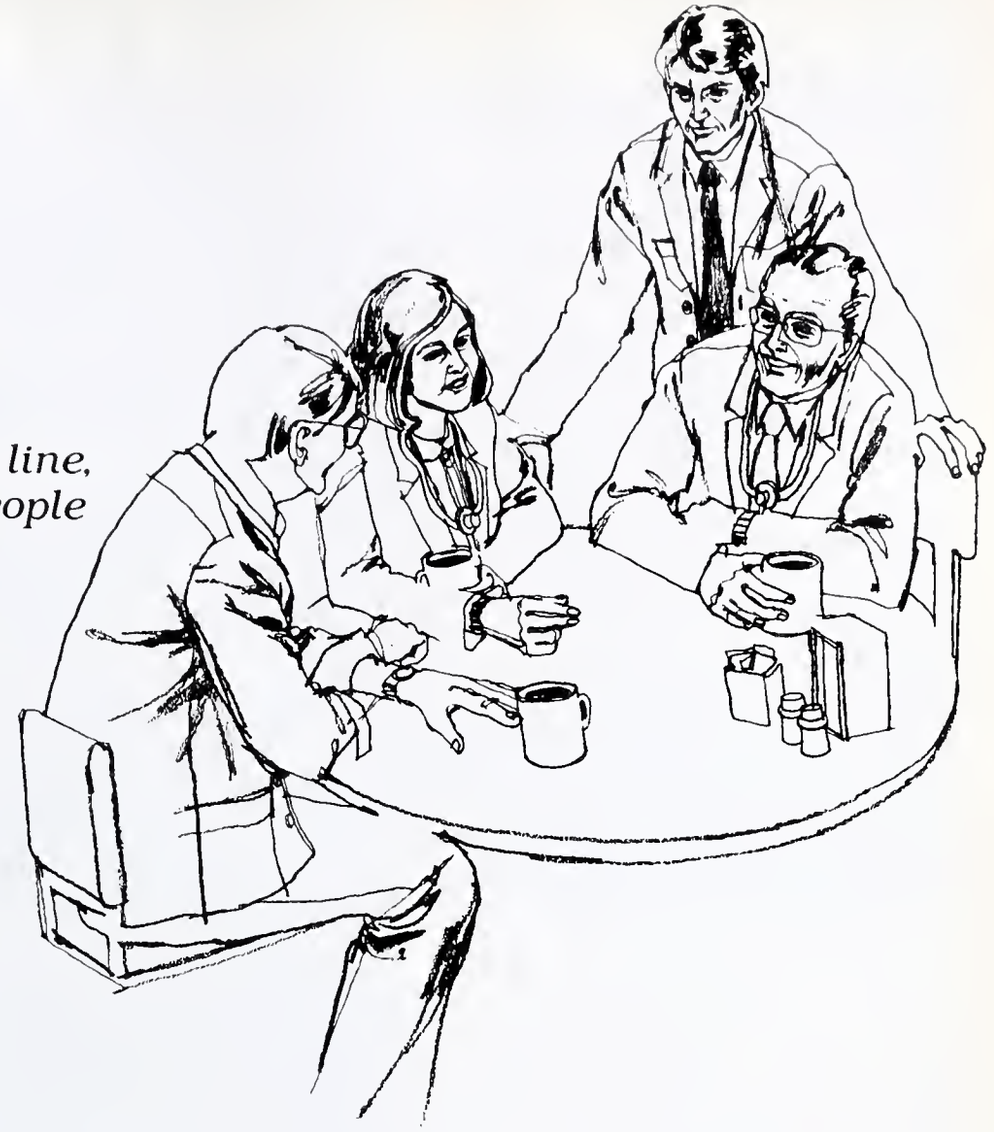
February 1-5—**OB/GYN Update—1987.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sunday-Thursday. Contact: UCD.

February 7-13—**Perinatal Medicine.** USC at Royal Lahaina Hotel, Hawaii. Saturday-Friday. 23 hrs. Fee: $525. Contact: USC.

February 8-12—**15th Obstetric Anesthesia Conference.** Ohio State University Hospital at Sheraton Waikiki Hotel, Hawaii. Sunday-Thursday. Contact: OSU Hospital, Dept of Anesthesiology, 410 W 10th Ave, Columbus, OH 43210. (614) 421-8487.

February 12-17—**42nd Annual Postgraduate OB/GYN Assembly of Southern California Hills.** Thursday-Tuesday. 28 hrs. Contact: OB/GYN As-

(Continued on Page 890)



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Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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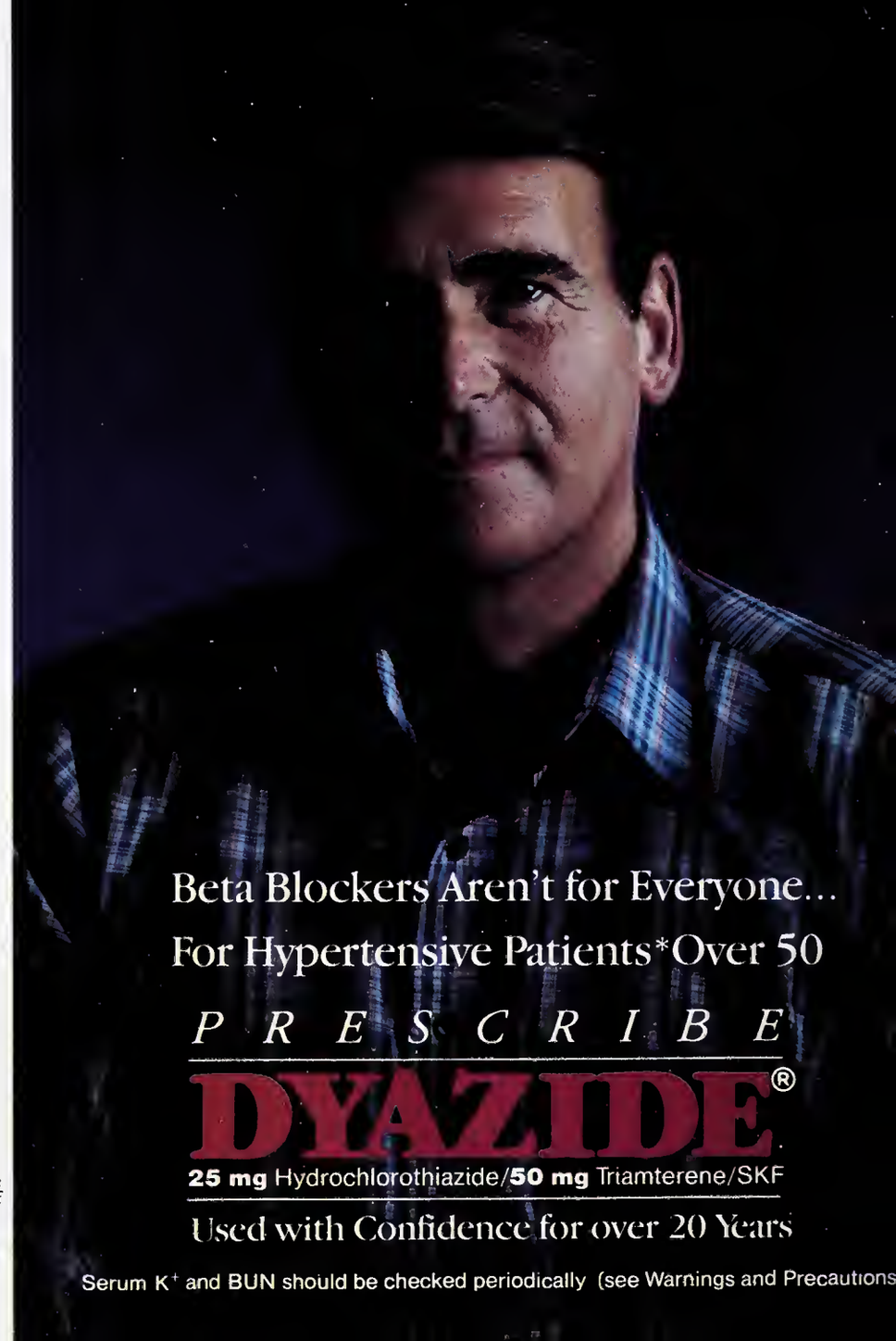

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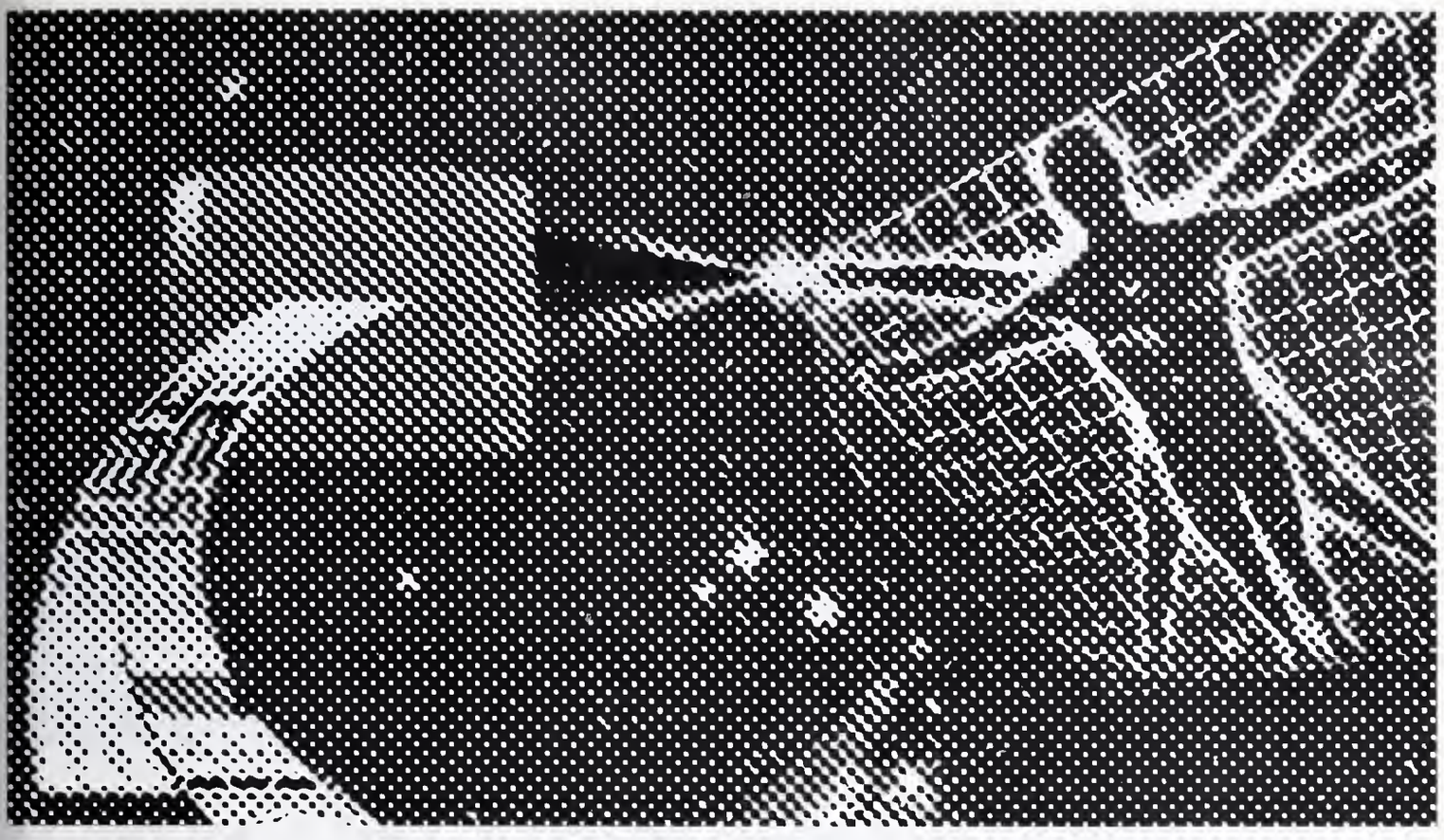


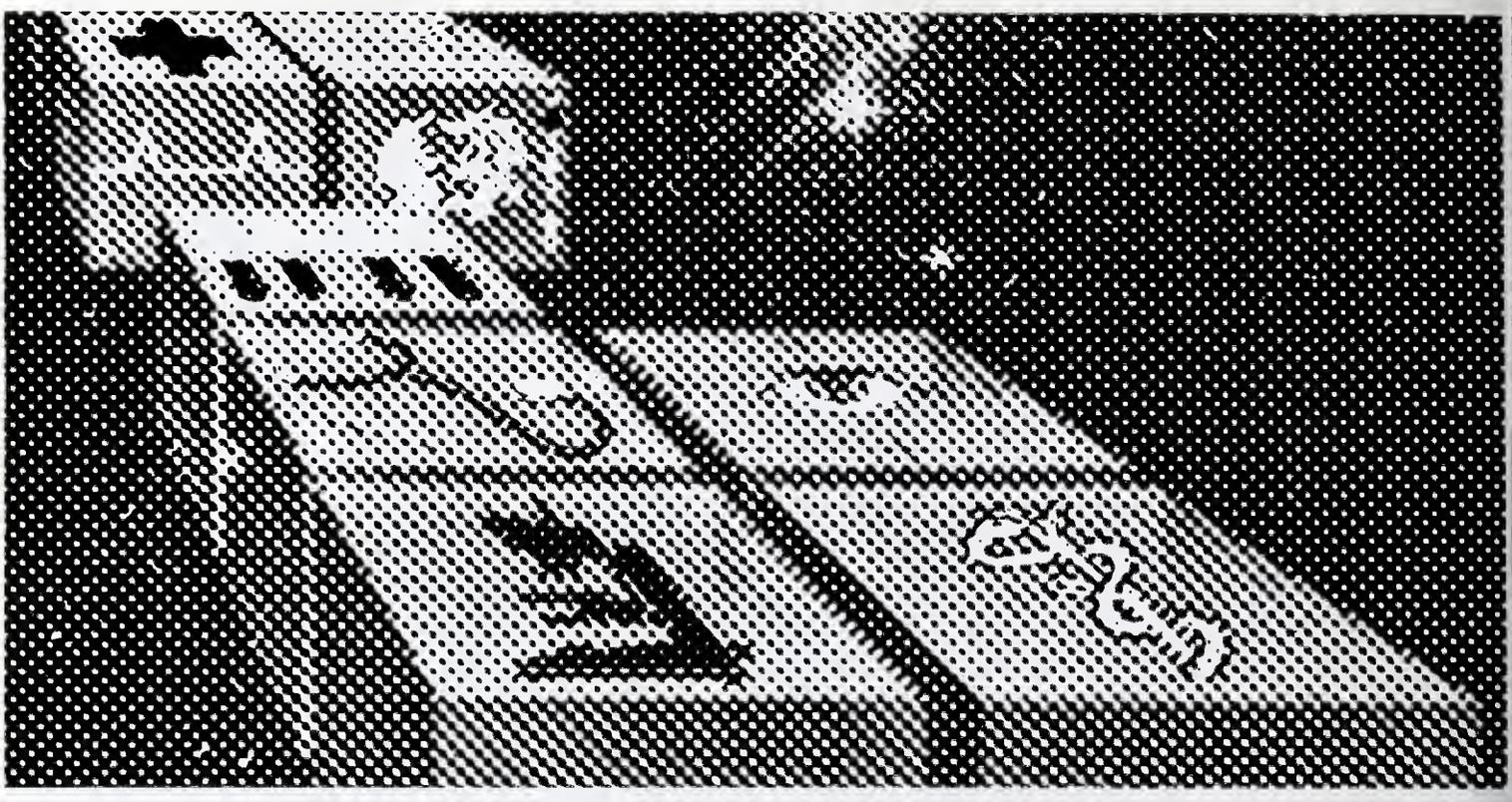
Medical Informatics

Once again the December issue of *The Western Journal of Medicine* is a special issue on a topic that the editors believe is, or soon will be, of importance for physicians. In recent years the subjects have been "high-tech" medicine (1985), personal health maintenance (1984), cross-cultural medicine (1983), occupational/environmental medicine (1982), geriatrics (1981) and cost of care (1980). Each year the special issue has been developed under the purview of a special editor with both a particular interest and a recognized competence in the field.

This year the editors have selected "Medical Informatics" as the topic for the special issue. The term "medical informatics" is coming into general usage among those who are interested in the capabilities, and potential capabilities, of new electronic methods of collecting, processing, storing, analyzing and using information to advance medical science and improve patient care. Physicians who already have their own computers, and use them as sources of medical information as well as for practice management, are at the cutting edge of what will surely be a new era in medical care. Many of them are no doubt quite familiar with the term "medical informatics." For those who have not yet joined this inner circle, it is hoped this issue will provide a window through which they can view some of what is going on in this important and relatively new field.

The journal is most fortunate to have Marsden S. Blois, PhD, MD, as Special Editor for this issue. Dr Blois is Professor of Medical Information Science and Dermatology at the University of California School of Medicine in San Francisco. He is current president of the American College of Medical Informatics. We are grateful to Dr Blois for using his knowledge, expertise and professional connections to assemble the fascinating and provocative papers that appear in this issue.

MSMW



What Is Medical Informatics?

When I was asked by Dr Malcolm Watts to join in preparing a special issue of *The Western Journal of Medicine* dealing with medical informatics, it occurred to me that there were timely reasons for doing so. Like many of my colleagues, I had spent a fair amount of time over the past few years trying to explain the meaning of "medical informatics." When it was decided to feature this subject in the December issue of the journal, this offered an unusual opportunity to *illustrate* what medical informatics is, and to put some of its best examples on display. It also seemed useful to draw attention to the important distinction between *information* (the commodity with which informatics deals) and the *computer* as a tool for use in processing this commodity. The computer continues to be an exciting object, it is increasingly present and it rarely fails to attract attention. Unfortunately, the commodity which is processed by the computer tends to be overlooked.

My acceptance of this assignment was also influenced by the expectation that my fellow members of the American College of Medical Informatics shared these sentiments and would be willing to join in this enterprise. This proved to be the case and I am grateful for the cooperation they promptly offered. Their willingness to prepare these papers resulted in the collection that you see here. Many of these contributions have been prepared by those who pioneered in the development of the topics of which they write.

The computer is increasingly being seen as one of the new symbols of medicine as we enter the 21st century. But how representative is it and how ought physicians view it? There are many ways in which the medical role of computers can be characterized. One is to look upon the computer as a mini-brain. Having been told that computers can do a few of the many

things that humans can, some physicians are perplexed and others misled. Since computers have neither sinew nor brawn, what must be intended by this remark is that computers can think. The model of the computer as a brain raises many interesting philosophical questions, but so far it has not proved to be a particularly productive way of thinking about what we ought to do with computers in medicine. I would rank this model behind applications in which computers are applied to processes in which the specifics are relatively well understood.

Alternatively, the computer can be regarded as a new kind of office machine. Viewing the computer as a species of the family *information machines* (having a far greater potential since they deal with information directly, but otherwise being similar in many ways to copying machines, desk calculators, dictating and communications systems) has been far more productive. This is the way in which they have been regarded in the commercial and industrial fields and, there, their impact has been revolutionary.

The major changes that they have brought about in medicine have thus far been in applications such as health systems management, clinical data management (patient records, laboratory, radiology and pharmacy systems), billing and accounting, imaging systems (computed tomography, ultrasound, nuclear medicine and magnetic resonance), process control and monitoring (signal processing in both the clinical and laboratory settings) and information retrieval and display (bibliographic search systems such as MEDLINE, and electronic journals and communications). These have been the bread and butter applications of computers to medicine and in many cases they closely resemble their nonmedical counterparts. In none of these cases does the computer do anything other than what the unaided human could in principle do, though in every instance by multiplying human labor by large factors, it transforms the practically impossible to the convenient. This is the model under which computers are making their greatest impact and where current developments are largely directed.

There is still another view of the computer's role in medicine and this is its promise as a novel research tool. The possibilities here can hardly be exaggerated. I would suggest that the computer in its relation to medicine is analogous to that of the microscope in the last century. The optical microscope was the tool that in the 19th century opened up entirely new domains of medicine. By revealing the previously invisible worlds of the structurally minute, it gave promise of understanding new processes: infection, immunity and much of pathogenesis. It was not the only tool required for this, but it was the key in achieving it. The analogous role that I believe the computer is now taking on is also that of a breakthrough tool—one enabling us to explore and better understand the informational and cognitive foundations of medicine. Its application to the classification and retrieval of data and to the management of information will result in a deeper insight into the structure of medical information and knowledge itself. In this role, it will provide us with a general means for enhancing the effectiveness of human inference (logical as well as statistical) and judgment, and find increasing use in both the clinic and the research laboratory.

Two generations ago, medical knowledge had only begun to be more extensive than what could be contained in a physician's head. In the interval between the two world wars, a crossover took place between the quantity of medical knowledge and the human capacity to remember. Earlier, medical educators could function by unthinkingly adding new information to the store of knowledge that medical students were expected to remember. Although the explosion of medical knowledge from the 1940s through the 1970s made this impossible, curriculum committees and licensing bodies were slow to recognize it. And the image of medical education as an exercise in memory, rather than one of reason, arose and has persisted even to the present.

And if neither the medical student nor the practitioner can now afford to randomly gorge at this feast of medical knowledge, neither can they ignore that which cannot be remembered. Selectivity and specialization have become successful adaptive strategies in both education and practice, though by themselves they do not address the underlying problem. The mass of unlearned or forgotten medical information has not disappeared nor has it become useless or irrelevant. Rather, what have now become necessary are better means of managing this information and locating it when needed. It is here that we have turned to computers and to information science for help. This is a major undertaking and a new adventure for medicine. Developments, such as those described here, continue to break new ground so that we can look forward to an increase not only in knowledge itself but in the means for analyzing, organizing and disseminating it.

Marsden S. Blois, PhD, MD
Special Issue Editor
Professor and Chair, Section on Medical Information Science
University of California, San Francisco
President, American College of Medical Informatics

Origins of Medical Informatics

MORRIS F. COLLEN, MD, *Oakland, California*

Medical informatics is a new knowledge domain of computer and information science, engineering and technology in all fields of health and medicine, including research, education and practice. Medical informatics has evolved over the past 30 years as medicine learned to exploit the extraordinary capabilities of the electronic digital computer to better meet its complex information needs. The first articles on this subject appeared in the 1950s, the number of publications rapidly increased in the 1960s and medical informatics was identified as a new specialty in the 1970s.

(Collen MF: Origins of medical informatics, *In* Medical informatics [Special Issue]. West J Med 1986 Dec; 145:778-785)

Computers, automobiles and telephones are now among the day-to-day tools of physicians. Starr credited the telephone and the automobile with the greatest improvements in the productivity of medical practitioners.[1] According to Starr, physicians were among the first to use telephone exchanges, built in the late 1870s, to connect with local drugstores and to communicate with patients requesting house calls. Automobiles were reported in the *Journal of the American Medical Association* in the early 1900s as being capable of cutting in half the time required for house calls and enabling patients to more readily visit physicians in their offices. Although Hollerith was working on punched cards for the 1880 census at the time Bell was beginning to market the telephone, it is quite evident that physicians have been much slower to adopt the computer than they were either the telephone or the automobile. Norberg estimated that in 1955 there were 240 computers in use, in 1974 there were 165,000 and in 1984 there were millions.[2] It is hoped that the plethora of computers in the 1990s will find physicians exploiting the full potential of medical informatics.

Origins of a New Name

The earliest references to any applications of electronic digital computers in medicine appeared in the 1950s in biophysics, bioengineering and biomedical electronics publications. New names appeared such as medical computing, medical computer science, computer medicine, medical electronic data processing, medical automatic data processing, medical information processing, medical information science, medical software engineering and medical computer technology. These terms were often used interchangeably, such as medical computer science for medical information science, as if what was processed—that is, information—was the same as how it was processed—that is, by computer. Yet, not until the early 1970s did it become clear that there was a need to settle on a name for this new domain of medical knowledge. To agree upon "medicine" or "medical" was not very controversial as any standard dictionary defines these terms as relating to or concerned with the research, teaching and practice of preventing, diagnosing or treating disease.[3] Some health professionals, however, prefer that the term "health" be broadly interpreted to not only include good health—the freedom from illness or disease—but also poor health—that is, being ill, sick or with disease.

To find a single term to include science, engineering and technology was more difficult. Harrison attempted to clarify "the confusion within the public, and also within the scientific community, as to the nature of science, engineering, and technology" and defined these terms as follows:

> Science is the process of investigation of physical, chemical, biological, behavioral, social, economic, and political phenomena. Engineering is the process of investigation into how to solve problems and includes everything the investigator does from the acceptance of the problem to the proof of the validity of the solution. Technology is the process of production and delivery of goods and services. Science drives engineering and technological innovation, but it is equally true that both engineering and technology drive science.

Harrison concluded

> It is the combined body of knowledge derived from the processes of investigation that are science, engineering, and technological innovation that has

From the Division of Research, Kaiser Permanente Medical Care Program, Oakland, California. Dr Collen is currently Scholar-in-Residence at the National Library of Medicine, Bethesda, Maryland.

This paper was prepared while Dr Collen was a Fellow at the Center for Advanced Study in the Behavioral Sciences, Stanford, California, and the work was supported in part by The Henry J. Kaiser Family Foundation. This article is based on material from "A History of Medical Informatics in the United States," a book in preparation for the National Library of Medicine, and is excerpted herein by permission of its Director, D. A. B. Lindberg, MD.

Reprint requests to Morris F. Collen, MD, 3451 Piedmont Ave, Oakland, CA 94611.

ABBREVIATIONS USED IN TEXT

AAMSI = American Association for Medical Systems and Informatics
ACM = Association for Computing Machinery
AFIPS = American Federation for Information Processing Societies
AIEE = American Institute of Electrical Engineers
AMIA = American Medical Informatics Association
CT = computed tomography
IBM = International Business Machines, Inc
IFIP = International Federation for Information Processing
IRE = Institute of Radio Engineers
LINC = Laboratory Instrument Computer
MEDINFO 74, 77, 80 and 83 = First, Second, Third and Fourth World Conferences on Medical Informatics
MEDLARS = Medical Literature Analysis and Retrieval System
MUMPS = Massachusetts [General Hospital] Utility Multi-Programming System
MIT = Massachusetts Institute of Technology
NCHSRD = National Center for Health Services Research and Development
NIH = National Institutes of Health
NLM = National Library of Medicine
SAMS = Society for Advanced Medical Systems
SCAMC = Symposium for Computer Applications in Medical Care
SCM = Society for Computer Medicine

become a resource of unprecedented value . . . There is no term in the English language to encompass this conglomerate of knowledge.[4]

Anderson at Kings College of Medicine (London) has documented the origin of the name "medical informatics":

As you will see from the book on "Education in Informatics of Health Personnel,"[5] we had been searching for some time before 1974 in the IFIP [International Federation for Information Processing] Technical Committee No. 4 to find a suitable term for the subject area. Professors Pages and Gremy of Paris were interested in at least two aspects being represented in the final term, namely, the French terms "informatique" and "automatique" that were used in France for medical information science or data processing. It was certain we had to find a new term for the book, and after much discussion we incorporated the words to form the name "medical informatics." We intended it to cover both the information and data parts as well as the controlling and automatic nature of data processing itself (J. Anderson, MD, written communication, May 1986).

It is noteworthy to a reader of the historic publication, produced by a working group of nine leading European medical educators, that they used the term "medical informatics" throughout the book and even formulated guidelines for a curriculum to teach medical informatics[5]; yet, nowhere in this book was this new term defined. In their discussion of this subject and how to teach it, however, it was apparent that medical informatics was meant to embrace all of the following: medical computing, medical data processing, medical information processing, medical computer science, medical information science, medical information systems, health care information systems, computer hardware and software, computer and information technology, applications of computers and data processing to the health services and basic concepts of computer science fundamental to medicine. As Anderson pointed out, the French literature had for ten years or more used the terms *informatique de médecine* or *informatique médicale,* and departments with these titles had been established in the 1960s in France, Holland and Belgium. The 1979 edition of *Harrap's New Standard French and English Dictionary* defined these French terms as follows: "*informatique*—information processing, data processing"; and "*informatique médicale*—medical computing."[6]

Although Anderson attributed the origin of medical informatics to the French, the Supplement to the 1976 *Oxford English Dictionary* credits the origin of the English word "informatics" to a translation from the Russian *informatika* and attributes its first definition to the following:

1967 FID News Bull XVII.73/2. Informatics is the discipline of science which investigates the structure and properties (not specific context) of scientific information, as well as the regularities of scientific information activity, its theory, history, methodology and organization.[7]

A search in MEDLINE of the National Library of Medicine (NLM) back to 1966 showed that articles in the French literature used the word *informatique* in 1968.[8] Another article in the French literature written in 1970 was entitled in English, "Study of an Informatic System Applied to the Public Health Services."[9] The next article found using the English word was published in 1972 in the Polish literature and was entitled "Informatics in Health Service."[10] A 1975 article in the Polish literature referred to *informatyki medycznej.*[11]

A search through NLM's MEDLARS CITE book catalogue found that the English term "medical informatics" first appeared in 1974 in the historic book already mentioned, the *IFIP Medical Informatics Monograph Series,* Volume 1, *Education in Informatics of Health Personnel.*[5] A search through DIALOG's* Modern Language Association International Bibliography (MLA BIB) back to 1968 showed that the word informatics appeared in the title of a Russan book as *informatika* in 1975.[12] The German literature used the term *medizinische informatik*[13]; however, the first German article written in English that used this term was published in 1977 with the title "Education in Medical Informatics in the Federal Republic of Germany."[14]

It is clear that Anderson's proposed new name "informatics" solved Harrison's need for a term to encompass science, engineering and technology,[4] and it freed this new field from all previous more limited names and notions. In the United States, the earliest definition of medical informatics appeared in the preliminary announcements distributed in 1977 for the Third World Conference on Medical Informatics (MEDINFO 80) in Tokyo, wherein I, as the program chair, defined the term: "medical informatics as the application of computer technology to all fields of medicine—medical care, medical teaching and medical research." Shortliffe at Stanford, however, emphasized that medical informatics included more than the applications of computers to medicine because some investigators in the field study the basic science of medical computing as a subject rather than as a tool.[15] He gave examples of studies in artificial intelligence that advanced medical information science, yet without any obvious application. In support of this view, Blois at the University of California, San Francisco, School of Medicine used medical information science to study and advance the theory and concept of medical information itself.[16] Although Yamamoto at George Washington University (Washington, DC) suggested it might be advisable to discontinue this search for a new name,[17] a committee of the Association of American Medical Colleges stated,

*Literature searches in DIALOG—PsycINFO (Psychological Information), EMBASE (formerly EXCERPTA MEDICA), MLA BIB, SOVIET SCIENCE AND TECHNOLOGY and ACA AM ENCYC (Academic American Encyclopedia)—were provided by Margaret Amara, Librarian, Center for Advanced Study in the Behavioral Sciences, Stanford, Calif.

Medical informatics is a developing body of knowledge and a set of techniques concerning the organizational management of information in support of medical research, education, and patient care. . . . Medical informatics combines medical science with several technologies and disciplines in the information and computer sciences and provides methodologies by which these can contribute to better use of the medical knowledge base and ultimately to better medical care.[18]

Ten years after the historic conference in France that resulted in the name "medical informatics," many of the original European and American participants again met to reconsider the term. Medical informatics was now broadened to include not only the device—that is, computer—and what the device processes—information—but also all medical research and development, education and medical practice, including physician assistance functions such as clinical decision support and expert consultant models.[19]

Although the standardization of medical terminology is very basic to medical informatics, not until 1985 did the American Society for Testing and Materials, which has served as a catalyst in the United States for developing and publishing voluntary consensus-based standards for a variety of products and systems (including computerized systems), establish a subcommittee on medical informatics.[20] This subcommittee is expected to develop an "official" definition of medical informatics. Until then, it is proposed that medical informatics be defined as computer and information science, engineering and technology in all fields of health and medicine, including research, education and practice.

Origins of the New Field

The everlasting quest of humans for information has resulted in the development of increasingly complex technology for counting, recording, storing, retrieving and communicating data. A computer is the obvious tool for these data-processing functions.

Goldstine at Princeton University (Princeton, NJ) attributed the concept of the electronic digital computer to Billings (the first Director of the National Library of Medicine) and its invention to Hollerith.[21] Billings, while Assistant Surgeon General of the US Army, was asked to assist the Census Bureau and to take charge of the work on vital statistics for both the 1880 and 1890 censuses. Hollerith was an engineer who graduated from Columbia University (New York) and went to work for the US Census Bureau in 1879.[22] The census was handwritten on cards that were then manually sorted into various categories and hand counted. To obtain additional information then required manually resorting and recounting. According to Goldstine, Billings conceived the idea of using cards that had data represented by notches punched into the cards, which could then be mechanically processed.[21] Billings asked Hollerith to work out a solution to this problem. The result was that Hollerith invented in 1882 a paper card with 288 locations for holes that ran under a set of contact brushes, completing an electric circuit when a hole was present. The punch card was devised by Hollerith to be equal to the size of a dollar bill to avoid having to manufacture new equipment. He also built machines for electronically punching and sorting these cards. Billings was a member of the census committee that decided to use the Hollerith punch-card system for tabulating the 1890 census. The census data on 62 million people were processed in three years. Hollerith went on to set up the Tabulating Machine Company in 1896, which became the International Business Machines (IBM) Corporation in 1924.

The First Digital Computers

The first all-electronic digital computer was invented by Eckert, Mauchly and their co-workers at the University of Pennsylvania (Philadelphia) in 1946. The computer was called ENIAC for Electronic Numerical Integrator and Calculator; it used 18,000 vacuum tubes as its active logic elements and had wired program plug boards and programming switches for storage.[23] Von Neuman in 1945 devised a method for storing programs—that is, instructions as distinguished from data—in a computer by an electrically alterable memory capable of storing both the instructions and the data to be used in calculations. In 1951 Eckert and Mauchly used von Neuman's stored program technology and built UNIVAC (Universal Automatic Computer) for the US Census Bureau for use in the 1950 census. This was the first computer to handle both numeric and alphabetic data, and it used magnetic tape drives to replace punched cards as a storage medium.

The second-generation digital computers, in 1958, used transistors instead of vacuum tubes and added magnetic-core storage memory designed by Forrester at the Massachusetts Institute of Technology (MIT, Boston). The third-generation computers appeared in 1963 in the form of solid-state integrated circuits consisting of hundreds of transistors, diodes and resistors embedded on tiny silicon chips, a process called large-scale integration.[24] This permitted the construction of a hierarchy of computers of different sizes. The IBM 360 series, introduced in 1964, was one of the earliest third-generation mainframe computers. Minicomputers, smaller in size and designed to do generalized though more limited tasks, were successfully marketed in the 1960s, especially by Digital Equipment Corporation as their Programmed Data Processor (PDP) series.

The First Personal Computers

Clark and Molnar in the Lincoln Laboratory of MIT in 1962 built a special-purpose Laboratory Instrument Computer (LINC) to maximize the degree of control over a computer by an individual researcher.[25] This was essentially a prototype personal computer with transistor circuitry, ferrite-core random access memory and magnetic tape storage, and it was small enough so that one person could assume complete responsibility for programming and operation, fast enough for simple on-line data processing while an experiment was in progress, logically powerful enough to permit more complex calculations later, if required, and with limited user-friendly features to facilitate training of persons unfamiliar with digital computers. The first personal computers were built in 1971 by Blackenbaker (called Kenbak I), and by Hoff of Intel Corporation (W. M. Bulkeley, "Who Built the First PC?" *Wall Street Journal,* May 14, 1986, p 31).[24] The fourth generation of computers, in the 1980s, exploits very-large-scale integration containing thousands of components on very tiny silicon chips. They have a greatly increased performance despite the smaller size and lower cost.

Programming Languages

Just as there evolved different generations of computers, so there developed different generations of programming languages and programs that made the hardware usable.[26] A language and its software can modify the character of a computer. A programmer writing in a computer's lowest level machine language is addressing memory cells, registers, adders and so forth. The circuitry of a computer recognizes only the electronic representation of binary numbers, and a program stored in a form that can be executed is in machine code and is a series of such numbers. Some of them represent instructions to the central processor, some of them are data and some are addresses in memory. A programmer using a higher level language works with variables, formulas and files. The most influential scientific programming language, FORTRAN (for *FOR*mula *TRAN*slation), was developed in 1957 by Backus and colleagues at IBM for scientific and numeric calculations.[27] COBOL (*CO*mmon *B*usiness-*O*riented *L*anguage) was created in 1960 by a joint committee of computer manufacturers and users and has long been the principal language for business and accounting functions in hospitals. BASIC (*B*eginners *A*ll-purpose *S*ymbolic *I*nstruction *C*ode) was developed in 1965 by Kemeny and Kurtz at Dartmouth College (Hanover, NH) as a language for introductory courses in computer science. LISP (*LIS*t *P*rocessing) was developed in the late 1950s at MIT by McCarthy; it structures both programs and data lists and has been widely used by researchers in artificial intelligence. One of the most widely used programming languages for medical application has been MUMPS (*M*assachusetts General Hospital *U*tility *M*ulti-*P*rogramming *S*ystem). This was developed in 1966 by Pappalardo, Marble and Barnett of the Laboratory of Computer Science, Massachusetts General Hospital (Boston) to meet the needs for a modular hospital information system.[28,29]

To allow communications between computers and to gather and integrate data from more than one computer site, it was necessary to develop computer and communication interfaces and build both local-area and wide-area networking systems. A local-area network connects on-site computers and peripheral devices, integrates departmental computing facilities and may connect with a supporting computer center. By 1971 prototype local-area networks of distributed minicomputers were being proposed in a hospital environment.[30] The US took the lead in developing wide-area networks for academic research, and in 1969 the Department of Defense's Advanced Research Projects Agency began a project called ARPANET. This successful national network has gradually been expanded and is the major component of the new National Science Foundation's network, connecting 60 major research universities in the country.[31]

The Diffusion of Informatics in Medicine

The current director of the NLM, Lindberg, identified the beginnings of medical informatics in the United States with the work of the first NLM director, Billings.[19] In 1879 Billings, who earlier had conceived the punch card (see above), initiated the *Index Medicus*, a monthly NLM publication, cumulated annually, that provides a bibliographic listing of references to current articles in the world's biomedical journals. It is not surprising that informatics should have been first diffused into the field of medicine by medical librarians and educators. A major contribution to medical informatics occurred when NLM initiated computerizing the *Index Medicus* with the printing of the 1964 edition and implemented the Medical Literature Analysis and Retrieval System (MEDLARS).[32] This placed NLM in the forefront of applying computer technology to bibliographic information needs. MEDLARS expanded with the addition of nationwide communication networks linking seven regional medical libraries in the country. MEDLINE (MEDLARS on line) was initiated in 1971 and contains files dating back to 1966. Anyone using the MEDLINE regional networks can search and retrieve by Medical Subject Headings, by words in the title or in the abstracts, by publication date or by journal article. MEDLINE has made a monumental contribution to computerized medical literature retrieval.

A search through all MEDLINE citation titles between 1966 and 1985 (1985 being incomplete) using the search words "medic: or health" with "comput:" for English only—that is, excluding articles in foreign languages—shows the increase in the number of citations through the years (Table 1), with a total of 2,440 citations. A similar search for these three words appearing anywhere in any journal article would find perhaps several times as many articles. A recent analysis by the Technical Services Division Staff of the National Library of Medicine of the articles in the general field of medical informatics in just three published annual proceedings—MEDINFO 83, American Association for Medical Systems and Informatics (AAMSI 84) and the Symposium for Computer Applications in Medical Care (SCAMC-84)—and in one recent full year of the journals *Computers in Biomedical Research* (1983 to 1984) and *Methods of Information in Medicine* (1984) yielded a total of 5,850 citations.[33]

The earliest peer-reviewed journals in medical informatics published in the United States were *Computers in Biomedical Research* (started in 1967), *Computers in Biology and Medicine* (1970), *Journal for Clinical Computing* (1972) and the American Medical Association's *Computers in Medicine* (1972). Books on medical computing began to appear in the United States in the early 1960s.[34-37]

TABLE 1.—*MEDLINE Search Counts (in English Language Literature Only) for 'Medic: or Health' and 'Computer:' by Year, 1966-1985**

Year	Search Counts	Year	Search Counts
1966	36	1976	117
1967	30	1977	118
1968	34	1978	155
1969	41	1979	165
1970	22	1980	187
1971	46	1981	181
1972	44	1982	248
1973	41	1983	307
1974	20	1984	324
1975	113	1985	211 (incomplete)

*Data provided January 1986 by J. Parascandola, MD, Chief, History of Medicine Division, National Library of Medicine.

Professional Medical Informatics Associations

In a rapidly evolving technology where substantive advances can occur within a year, publications in traditional medical journals are often out-of-date, and books, by the time they are published, may describe obsolescent technology. Accordingly, the timeliest articles on computer applications to medicine often have been found in proceedings and transactions of meetings sponsored by professional associations and industry.

The Professional Group in Bio-Medical Electronics of the Institute of Radio Engineers (IRE) was organized in 1951 and in the 1950s was "the largest professional organization which is concerned with the broad area between the biological and medical field and the engineering and physical sciences."[38] It sponsored annual conferences in biomedical electronics and published the *IRE Transactions on Medical Electronics*, which in the 1950s was the main outlet for papers in biomedical computing. A 1955 review of the "progress of medical electronics" gave credit to the American Institute of Electrical Engineers (AIEE), later to become the Institute for Electrical and Electronic Engineers, for also sponsoring some of the earliest meetings on this subject.[39] The Association for Computing Machinery (ACM) was formed in 1947[40] and established its Special Interest Groups in 1960, one of which was Biomedical Computing (SIG BIO), which also provided an outlet for early articles on bioengineering. AIEE and ACM, with participation by the National Simulation Council, sponsored joint computer conferences, the first being held in 1951 (R. B. Frost, "NCC [National Computer Conference] at the Crossroads," *Datamation*, Jun 15, 1986, pp 169-172). At their fall Joint Computer Conference in 1961, these professional associations formed the American Federation for Information Processing Societies (AFIPS). AFIPS has been the US representative to the International Federation for Information Processing (IFIP).

The term "informatics" became internationally accepted as a result of its use by IFIP for its triennial international congresses for medical informatics (MEDINFO). The Fourth Technical Committee of IFIP organized MEDINFO 74, the First World Conference on Medical Informatics, held in Stockholm in August 1974. It is noteworthy that the term "medical informatics" appeared in the title of the proceedings of this congress and in only one paper by its originators.[41] MEDINFO 77, the Second World Conference on Medical Informatics, was held in Toronto in August 1977; the term "medical informatics" appeared in five articles in its proceedings. In the Third World Conference on Medical Informatics held in Tokyo in September 1980, only four articles in these proceedings contained the term "informatics." MEDINFO 83, the Fourth World Conference on Medical Informatics, was held in Amsterdam in August 1983, and the term "medical informatics" appeared in nine papers in its proceedings.

Conferences on Medical Informatics

The largest conferences in the United States completely dedicated to medical informatics have been the annual meetings of the Symposium for Computer Applications in Medical Care (SCAMC). The first SCAMC was held in 1977; since then SCAMC has been held annually in the fall on the East Coast. The Society for Advanced Medical Systems (SAMS) was organized in 1971 for the purpose of furthering medical systems, including computing systems, and it published the proceedings of its first annual meeting that year (D. Davies, "AAMSI's Forebears," *AAMSI News* 1985; 4:1-2). Its original focus was multiphasic health testing systems, but soon the major interest turned to medical computing systems. The first professional organization in the country committed entirely to medical informatics was the Society for Computer Medicine (SCM), also organized in 1971. SAMS joined with SCM to hold a joint conference in 1982,[42] and the result of this union was the American Association for Medical Systems and Informatics (AAMSI), which held its first annual conference in 1982.[43] The first conference in the United States that contained the words medical informatics in its title was held in 1982 in San Francisco; it was called the First Congress of the American Medical Informatics Association (AMIA Congress 82).[44] The idea for the AMIA Congress 82 developed during MEDINFO 80 in Tokyo, when some US participants decided to emulate the MEDINFO model of the International Medical Informatics Association. AAMSI took over the sponsorship of this congress on medical informatics in 1983 and has since conducted an annual spring AAMSI congress on the West Coast. In 1985 the American College for Medical Information was established to advance the field of medical informatics and to recognize experts in the field.

Professional, special-interest users groups have been very influential in diffusing medical informatics, especially for software. The MUMPS Users' Group began its annual meetings in 1972 and has grown to represent one of the largest groups of medical users of a specific programming language in the country. AAMSI has had several professional specialty groups (PSGs) interested in various medical computer systems and applications. In 1964 hospital users of IBM systems organized the Electronic Computing Health Oriented (ECHO) organization that since then has held regular meetings and shared the experiences of more than 1,000 hospitals.[45] Hardware vendors such as IBM and Technicon helped to advance early research and development in medical computing by supporting periodic conferences. The first IBM Medical Symposium was held in 1959 in Endicott, New York; these continued for ten years to be informative meetings for medical users of IBM computers. Technicon similarly sponsored a series of annual meetings on computer applications to clinical laboratories, beginning in 1965.

Informatics in Medical Research, Education and Practice

To support the proposed definition that medical informatics is computer and information science, engineering and technology in all fields of health and medicine, including research, education and practice, the outline given in Table 2 may be helpful.

The earliest published papers in medical informatics appeared in the 1950s when computer science was applied to biomedical research for simulation models and electrophysiology.[46-50] Later, the LINC computer's advanced engineering was exploited by medical researchers (*Wall Street Journal*, May 14, 1986, p 31),[24] and the ARPANET technology permitted medical researchers throughout the nation to work together.[31]

In medical education, information science soon permitted

TABLE 2.—*Some Early Examples of the Diffusion of Informatics in Medicine*

Medicine and Health	*Computer and Information*		
	Science	*Engineering*	*Technology*
Education	Case simulations	MEDLARS	MEDLINE
Research	Computer modeling	LINC	ARPANET
Practice	Computer diagnosis	Information systems	CT scanning

CT = computed tomography

teaching students with the use of computer simulations of case studies.[51-54] Information engineering produced the MEDLARS versions of the *Index Medicus*, and further advances in technology resulted in on-line literature retrieval by MEDLINE.

In medical practice, computer science attempted early to provide support in medical decision making and diagnosis. Hardware and software engineering produced a variety of medical and hospital information systems, and computer technology put computed tomographic (CT) scanning into most hospitals in the country.

In the United States, the early development and evolution of medical informatics was almost entirely supported by government grants and contracts. In 1960 the National Institutes of Health (NIH) established an Advisory Committee on Computers in Research that was responsible for the initial funding of many of this nation's leading academic centers in medical informatics.[55] NIH established its own computer center on campus and a Division of Computer Research and Technology.[56] In addition, other institutes, such as the National Institute of General Medical Sciences, supported projects involving the automation of clinical laboratories and the development of automated aids to diagnosis.[57] The National Heart and Lung Institute supported projects on modeling cardiovascular and respiratory physiology and the automated analysis of the electrocardiogram. It became apparent that the NIH categoric institutional structure was not particularly well suited to providing support for biomedical research tools, so in 1962 a separately budgeted special resources branch was established in an independent Division of Research Resources to provide funds for biomedical research computing facilities. In the 1960s, biomedical computing facilities were established in 45 universities, 6 hospitals and 4 research institutes throughout the US.[58]

Health Services Research Centers

Under the Heart, Cancer and Stroke Act of 1965, Regional Medical Program grants were authorized by the US Congress. By 1967 there were established 54 Regional Medical Programs, including clinical laboratory systems, clinical data collection studies, multiphasic screening systems and tumor registries.[59] In 1967 the National Center for Health Services Research and Development (NCHSRD) began to fund Health Services Research Centers, two of which— Kaiser Foundation Medical Centers, Oakland and San Francisco, California, and the University of Missouri-Columbia School of Medicine, Columbia, Missouri— had health care technology, including information systems, as their primary focus.[60]

Although in the 1960s, courses on digital computing were usually included in the curricula of bioengineering, usually within schools of electrical engineering,[38] the first academic department in the United States for teaching computing in medicine was established in 1960 at Tulane University School of Medicine (New Orleans), and Sweeney was designated as its first Professor of Computer Medicine. When asked what this title meant, he would jokingly counter, "Does this mean that I treat sick computers?"[61] In other American universities to follow, they were generally called Departments of Medical Information Science. Whereas in Europe the earliest "medical informatics" departments appeared in France, Belgium and the Netherlands, the first "Department of Medical Informatics" in the United States was established by Warner in 1986 at the University of Utah School of Medicine (Salt Lake City). (This information was gleaned from the masthead page of the February 1986 issue of *Computers and Biomedical Research*.)

An early example of a substantial effort to exploit computer and information science to improve medical practice was in computer-aided diagnosis. Although this area of medical informatics has continued to evolve through several stages of research and development, for both education and practice, its ultimate objective is to support the clinical practice of medicine. The first conference reported to be devoted solely to the problem of diagnostic data processing was held in Rockefeller Center (New York) in January 1959.[62] At this conference, most papers reported on the use of statistical probabilistic approaches to computer-aided diagnosis. Although sometimes achieving excellent diagnostic performance, these were constrained in scope and not sufficiently consistent with traditional clinical practice to be accepted by clinicians. By the 1970s, approaches more closely emulating the usual clinical decision-making process were sought and artificial intelligence methods began to be used for differential diagnosis and specialty medical consultation.[19,63]

Undoubtedly the broadest engineering applications of informatics to medicine have been in diffusing information systems into hospitals, clinics and their clinical support and ancillary services. In addition to Health Services Research Centers, the NCHSRD initiated grants and contracts to fund a variety of information systems in the 1960s. The status of NCHSRD-supported computer-based information systems at its peak of support in 1969 was summarized in a report that mentioned some of the following projects as being operational and providing patient care functions[64]: medical records projects, hospital information systems, clinical laboratory systems, x-ray information systems, physiologic monitoring systems, pharmacy information systems, a multiphasic screening system and patient interviewing projects. The NCHSRD report concluded that the then-available time-sharing computing technology could not support simultaneously the many divergent and data-rich requirements of services that existed in any relatively large hospital. What was technologically required was the development of a computer system that could adapt to an unevenly evolving need for computers among the several services in a hospital rather than a total frontal attack on all hospital services. The report predicted that networking computers would have more potential for the evolvement of hospital information systems than an attempt to solve the problem with one very large machine.

In graphics technology, the use of an electronic digital computer to plan dosage schedules for irradiation therapy for

cancer patients was reported as early as 1958,[65-67] and computer dosage planning for irradiating cancer patients soon became a routine procedure.

The first clinical prototype x-ray head scanner was developed in 1971,[68,69] and CT scanning technology was subsequently applied to ultrasound, radionuclide, positron emission and nuclear magnetic resonance images. CT scanning was called "the most important technical development in diagnostic radiology since the introduction of image amplification."[70]

A 1965 survey of the state of computer-based information systems for medicine in the United States listed 73 projects in hospital and clinic information systems, 51 projects in computer-aided diagnosis and 28 projects in storing and retrieving medical documents and information.[71] Other useful collections of articles for these first ten years of computer applications to medical practice can be found in the July 31, 1964, issue of *Annals of the New York Academy of Sciences* entitled "Computers in Medicine and Biology," and in the *Journal of Chronic Diseases*, volume 19, 1966. In addition, two books were published in 1965 that provide excellent reviews of the accomplishments of the first ten years of medical informatics.[72,73]

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The National Library of Medicine and Medical Informatics

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Medical informatics attempts to provide the theoretic and scientific basis for the use of automated information systems in biomedicine. Even though a new field, its roots are in the 19th century. The National Library of Medicine (NLM) began classifying the medical literature and publishing the Index Medicus *in 1897; in the early 1960s, the growth of the index gave rise to MEDLARS, the first successful, large-scale, computerized bibliographic system. In 1971, about the time MEDLARS evolved into a nationwide on-line retrieval system known as MEDLINE, a committee of the Association of American Medical Colleges published a report calling for the NLM to exert strong leadership in developing computer applications for information transfer in medicine. The NLM has sponsored several training and research programs in this area and is now developing the concept of "centers of excellence" in medical informatics. In addition, there are a number of current research and development activities within the NLM internal and extramural programs that may influence the progress of medical informatics.*

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Medical informatics, a new, multidisciplinary field, attempts to provide the theoretic and scientific basis for the use of automated information systems in biomedicine. Investigators come from health and computer sciences, engineering, library and information science and management

Like many new fields, especially in medicine, the initial practical demonstrations of the power of the methods of medical informatics (in this case, to store and retrieve information, to compute quantities and to control events) precede and overshadow its incomplete theoretic base. Nonetheless, this field is already having a profound effect on health care affairs because of its focus on the fundamental processes of human medical treatment and information. Thus, studying the processes of teaching and learning the accumulated record of scientific evidence and discovery, the general problems of patient record-keeping and the processes of medical diagnostic and management decision-making has been of greater interest to those in medical informatics than issues particular to the individual specialty areas of medicine and health care per se.

For example, the use by a surgeon of information from statistical studies of populations along with incomplete sets of laboratory, roentgenologic, scientific and clinical information about a single patient to form the basis for the surgeon's decision to operate has been of great interest in medical informatics. Sohn, Robbins[1] and de Dombal[2] have reported the results of such studies. These are examples of the general clinical problem of making decisions in the face of uncertainty. Such a dilemma has since the beginning of medicine placed a premium on learning, on skills in reasoning and on empathy. Since the beginning of modern scientific medicine, there has been a premium, too, on the thoroughness of a physician's knowledge and his or her familiarity with the rapidly changing understanding of disease processes and the discovery of new treatments and preventatives.

The National Library of Medicine (NLM) has for 150 years been dedicated to organizing the knowledge of medicine and to providing timely information to health professionals in support of clinical health care and research. More recently, NLM has also taken a strong interest in the cognitive processes and systems with which such knowledge is used in timely and appropriate ways to improve health. Some aspects of this evolution may be of interest to readers.

The National Library of Medicine has the legislative mandate

to assist the advancement of medical and related sciences, and to aid in the

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ABBREVIATIONS USED IN TEXT

AAMC = Association of American Medical Colleges
GRACE = Graphic Arts Composing Equipment
MEDLARS = Medical Literature Analysis and Retrieval System
MeSH = Medical Subject Headings
NLM = National Library of Medicine

dissemination and exchange of scientific and other information important to the progress of medicine and to the public health.[3]

Early NLM Development

Indeed, it was in the pursuit of this purpose that John Shaw Billings, MD, in 1879 started the *Index Medicus*, "A monthly classified record of the Current Medical Literature of the World." In his prospectus, Billings described the new index as follows:

In its pages the practitioner will find the titles of parallels for his anomalous cases, accounts of new remedies, and the latest methods in therapeutics. The teacher will observe what is being written or taught by the masters of his art in all countries. The author will be enabled to add the latest views and cases to his forthcoming work, or to discover where he has been anticipated by other writers, and the publishers of medical books and periodicals must necessarily profit by the publicity given to their productions.[4]

The first issue of *Index Medicus* listed 18,000 articles. Within 50 years its annual coverage had tripled. Today the annual coverage exceeds 250,000 articles. By the early 1950s the logistics of maintaining the *Index Medicus* had become overwhelming. Currency could not be maintained and backlogs were growing rapidly.

In 1960 a new system was put into operation that handled 125,000 citations with multiple entries for each. The system used tape-actuated typewriters to repetitively print a unit record across the top of a Hollerith card, the keypunching of filing indicia into a reserved area of each card, sorters and collaters to arrange the cards into appropriate author and subject subsets and a high-speed rotary-step camera. The camera, capable of varying its aperture to fit the number of lines in an entry, would photograph the cards on filmstrips that could be cut into column length.

The Creation of MEDLARS

This early application of "automation" foreshadowed what might be done and led to the specifications of the Medical Literature Analysis and Retrieval System (MEDLARS). It was this system that produced the January 1964 issue of *Index Medicus*. A machine called GRACE (Graphic Arts Composing Equipment), developed specifically for the NLM, typeset pages at the rate of 300 characters per second. GRACE accepted input directly from magnetic tape that had been reworked by a computer into a page-block format.

This photocopier tape contained a matrix of 226 characters etched on glass. These characters were in several sizes and fonts, with a complement of diacritical marks. Behind each character on the matrix was a high-speed flash tube; the circuitry of GRACE timed the flashing of these lights. Between the matrix plate and a 9-in wide roll of film, there was a mirror and reciprocating lens that constantly roved back and forth, photographing one line of characters, character by character, across the entire width of a three-column page. It may be calculated that, at 1.7 seconds per sweep, GRACE had to labor for 150 hours to compose the five volumes and 8,900 pages of the 1968 *Cumulated Index Medicus*.

Remarkable for its day, GRACE was a significant step in computer-controlled typesetting. By showing that such a system was operationally feasible, NLM created the precursor, if not the stimulus, for computer-based publishing. This was recognized by GRACE's retirement in 1969 to the collection of the Smithsonian Institution.

But MEDLARS was not designed solely for the publication of *Index Medicus*. From the beginning, retrieval was prominent in its specifications. By the late 1960s, around 16,000 searches a year were being done in batch mode on three computers that mounted the MEDLARS tapes. MeSH (Medical Subject Headings) had been thoroughly revised and greatly expanded. This structured, controlled vocabulary permitted in a computerized search a far greater specificity than was possible through the use of the *Index Medicus* main headings.

The newly formed Lister Hill Center soon began experiments with interactive on-line searching using the teletypewriter communication network (TWX) and an abbreviated file of 100 clinical journals called Abridged Index Medicus—thus the name AIM-TWX. The extension to the full *Index Medicus* file and the utilization of common communication carriers soon followed, and MEDLINE was launched. The immediate and remarkable success of MEDLINE provided a great stimulus to the common carriers to rapidly expand the coverage of their telecommunication networks. This contributed greatly to the early introduction of on-line searching of many other subsequent data bases.

The on-line interactive search made the rapid identification of citations a practical reality. But citations were not the answer to a searcher's question. For that one needed the documents to which the citations referred. To assure the availability of documents, NLM, under the aegis of the Medical Library Assistance Act of 1965, supported new library construction, collection development, training and special publications.

Perhaps most important of all, however, the Act extended to NLM authority to establish a national communications system, including, if necessary, construction of NLM branch libraries in the states and construction or reconstruction of libraries at the medical schools. Fortunately, this authority was used wisely to build up strong local and regional libraries and to build the Regional Medical Library network that we know today.

In this system, documents that were not available at a hospital library could be requested from larger resource libraries and a Regional Medical Library. If the material sought was not available there, NLM acted as the library of last resort. In 1985 more than 2 million documents were delivered within the network. NLM had to supply only 160,000 of these. This network-routing system is being even more fully automated. A national computer-based system for interlibrary loan requests (DOCLINE) is now being implemented in stages throughout the nation.

Medical Education

While the Lister Hill Center was beginning to engage in experiments in telemedicine supporting health care delivery and medical education using the Advanced Technology Satellites ATS-1 and ATS-6, the NLM contracted with the Association of American Medical Colleges (AAMC) to assess the

future role of computer and communications technology in medical education and health care delivery. The report of the AAMC committee, chaired by Eugene Stead, MD, was published in 1971. The committee wrote with regard to computers in medicine

> that the time has come for the Lister Hill Center to exert strong leadership in the development of the computer science field as it relates to medical education and the preparation of professionals for the delivery of health care. . . . The committee believes that we will have to reexamine the problems in medical education and practice and devise solutions utilizing computer technology which will offer new approaches to education and give new patterns for professional staffing of clinical units, for the collection of clinical and laboratory data, and for clinical decision making.[5]

These recommendations led to a revamping of the intramural programs of the Lister Hill Center and to the establishment of a series of research, training and career development grants in what was then called "Computers in Medicine."

In 1971, the vast majority of academic health centers barely tolerated such endeavors. There was no locus for such activity, and, indeed, there was little recognition that such a field existed. It certainly had no name. Not even the people working in the field could agree on what it should be called, let alone what it encompassed. Years later, the name "medical informatics" was adopted.

For these reasons the training grants had as their primary stated objective the training of established faculty members who could return to their institutions not so much to research careers in medical informatics—although that, of course, was not discouraged—but rather to improve the environment and to help create a greater institutional receptivity for the increasing use of automated systems in all phases of medical education and health care delivery. The research and career development grants, on the other hand, were designed to support and enhance the careers of those few existing research workers in the field.

The extent to which the training grants accomplished their avowed purpose is difficult to assess definitively. These efforts, the emergence into prominence of general information systems and microcomputers and the rapid introduction into medicine of computer-mediated technology such as the computed tomographic scan all contributed to a radical change in environment in the decade that followed. Because of that change, the training grants were changed in 1982 to research training grants with the specific purpose of training future researchers in the field.

Related to this, the NLM has recently proposed the development of centers of excellence in medical informatics.

Centers of Excellence

Don E. Detmer, MD, Vice President for Health Sciences, University of Utah School of Medicine (Salt Lake City), views the center of excellence as "an institutional locus for the education of health professionals and medical informatics experts in the techniques and problems of using computers and information systems to improve health care."[6] Jean Mayer, PhD, President of Tufts University School of Medicine (Boston), in proposing centers of excellence in medical informatics describes them as providing "a highly productive research and scholarly environment with the status of a division or department in a medical school."[6]

However it is described, this organization would have three major functions: coordinating medical informatics studies and skills into the overall curriculum; conducting research in medical informatics, and training and educating in the field. Such centers of excellence will substantially enhance the recognition and career development so badly needed in the field.

Yet, it is not only the environment for medical informatics that has been changing dramatically. The very boundaries of clinical medicine are rapidly being pushed back to the molecular level, and with that development has come an explosion of automated data bases. As the volume of medical information has rapidly expanded, access to that information has become more and more constrained by the system that housed it. The utility of information to a very large extent depends on the ease with which it can be retrieved. Two great bottlenecks to information retrieval are the difficulty of human-to-machine and machine-to-machine communication.

Knowledge Representation and Medical Informatics

In the late 1950s, the modern NLM classification system, MeSH, was rebuilt. It combined through a common set of pointers the indexing of articles and cataloguing of books and monographs. This controlled, highly structured, knowledge representation scheme is a very powerful tool for retrieving citations to the medical literature. Its structure and "explode" capability make it possible through single entries to retrieve a wide range of related material. The in-depth indexing (an average of 12 terms assigned per article) and the use of Boolean manipulators ("and," "or" and "and not") make possible precise retrieval. But the system is complicated and was originally designed for relatively well-trained users. Indeed, at first the training period for MEDLARS searchers was three months. While this has been greatly shortened, the vast majority of searches are still done by trained intermediaries.

GRATEFUL MED

Numerous attempts have been made by NLM and others to simplify this machine interface so that the system may be used by nonexperts. For certain types of searches these systems are very effective. NLM's user-friendly connection to MEDLINE, called "GRATEFUL MED," provides a transparent, menu-driven use of Boolean operators "and" and "or" with free language entries that are searched both as free text and as MeSH-controlled vocabulary.[7] Even in its simplest form, using only selected features of the power of the MEDLARS system, it will retrieve enough relevant citations to satisfy many queries. On the other hand, more experienced users can operate through another mode of GRATEFUL MED to bypass the menus and have all the power of MEDLARS command language searching restored. We believe GRATEFUL MED will also be helpful to persons who wish to learn more about information-retrieval issues and to improve their skills in searching through a gradual and self-controlled tutorial process. Successive versions of this front-end search system are already being tested. Version 2.0 incorporates much of the Medical Subject Headings thesaurus of index terms. This is designed to assist biomedical inquirers to "map" their idiosyncratic or specialists' inquiries to the (often-more-general) MeSH terminology to obtain access to the larger number of scientific articles that are indexed under standard index terms.

GRATEFUL MED already includes a simplistic algorithm that suggests possible improvement in phrasing a user's search statement. It seems likely that future versions will offer advice to users that is an increasingly intelligent equivalent of the assistance of an expert reference librarian. (GRATEFUL MED is available for $29.95 [1986 price] from the National Technical Information Service, United States Department of Commerce, Springfield, VA 22161; order number PB86-158482.)

MICRO-CSIN

An obvious improvement in user-friendly front ends is for them to be able to communicate with more than one data base. MICRO-CSIN (Chemical Substances Information Network) is such a system. It knows the protocols and can, therefore, automatically log into any of the hundreds of data bases available from nine main vendors. Because its basic purpose, as the name implies, is to search chemical systems, cross-data-base searching is reasonably effective. This machine-to-machine communication is facilitated by the presence of unique identifiers in chemistry such as the chemical name and the Chemical Abstracts Service registry number. These unique identifiers make it possible to find the chemical of concern regardless of the data base and the data-base structure. A small number of key concepts, such as toxicity, physical and chemical properties and so forth then make it possible to retrieve the record of interest. This system, too, offers many opportunities for improvement through adapting the growing understanding of informatics principles. Systems such as MICRO-CSIN do not, for example, really "know" a user, much less his or her educational level, state of urgency in making the request or basis in having (perhaps recently) received other information from the system. Such possibilities for systems to do "user profiling" are still only research possibilities, even though the fundamental concepts involved are easily understandable at the common-sense level.

Unified Medical Language System

Unfortunately for most of biomedicine, there are no unique identifiers. Even where data bases have a shared subject domain, they use different knowledge representation schemes, different indexing philosophies and different vocabularies. In these instances, transferring a concept from one data base to another is extremely uncertain, being subject to all the vagaries of normal discourse without a human to interpret them. There are three possible solutions to this problem: adopt a standard vocabulary, interpose an "expert" system that simulates a human intermediary or create some canonical knowledge representation scheme into and from which all others can be transposed.

The NLM believes the first to be unacceptable to the community. A combination of the second and third is being studied with the help of the academic community and professional societies. This combination has been called a "Unified Medical Language System." It is viewed as a long-term (and costly) project from which many intermediary benefits may be derived in the course of its pursuit. The NLM has received congressional support to coordinate this effort. Resources from five universities have been contracted for, and a significant NLM staff effort has been started. The American Medical Association has agreed to coordinate the involvement of professional societies.

The rate of increase in biomedical knowledge makes it impossible for any one person to be truly up to date. One of the greatest challenges of the information age is to create effective syntheses that can be maintained automatically. The traditional medical syntheses of books and monographs are now almost always substantially out of date before they are printed. Review articles are somewhat better, but in the absence of some updating mechanism they, too, are soon out of date.

Hepatitis Knowledge Base

The National Library of Medicine in 1979 built a prototype "hepatitis knowledge base" aimed at providing up-to-date information needed to support daily diagnostic, prognostic and management decisions.[8] The hepatitis knowledge base was designed to provide substantive information relevant to a wide variety of questions rather than citations to the literature that may contain such information. The information in the knowledge base was hierarchically arranged to provide increasing detail and specificity, including citations to the primary publications on which the syntheses were built. For this limited domain, the structure of the hepatitis knowledge base was, indeed, a knowledge representation scheme.

Expert Systems

In a related area, the NLM has supported intramurally and by grant the development of knowledge-based "expert systems." They have in common the components of a knowledge base and an "inference engine." To a varying extent, each expert system may model human cognitive processes in such areas as medical diagnosis and patient management. In all these cases the knowledge base is constructed on some representation scheme (often sets of production rules) and represents a kind of synthesis for that domain. Updating and maintaining such syntheses remain important problems for which no adequate machine solution has yet been devised.

Image Processing

In the foregoing discussion of NLM and medical informatics, we have attempted to suggest the progress of the solutions to the problem of providing health scientists with the information they need when they need it and in a format that can be readily used. We have, however, dealt only with information represented by symbols—that is, words, numbers and so forth. Much medical information resides not in symbols of language but in images. Therefore, NLM also supports research in image processing.

The traditional problems of storage, indexing and retrieval are in the case of images compounded by problems such as color fidelity and resolution. Modern technology such as optical disc storage and digitization of images suggests enormous possibilities in the effective use of information from images. Perhaps the main bottleneck resides in indexing. Verbal labeling of images sacrifices an enormous amount of information. This makes retrieval very inefficient except in its simplest form. One can visualize retrieving information from and across images based on spatial clusters in a digitized format. Indeed, the digitization of the images makes possible the three-dimensional projections that conform to reality. Because much of the imaging of modern medicine—computed tomographic scans, nuclear magnetic resonance and the like—is digital from the beginning, this description is not a speculation about the future but rather a view of the present.

Institutional Settings

But solving the technical problems of knowledge representation, unified medical language systems and machine-to-machine communication is not all that is required. Institutional restructuring to manage effectively the complex information activities within health centers must also occur. For that reason, NLM instituted in 1983 a program to support the study, planning and effectuation of Integrated Academic Information Management Systems.[9] This program was initiated with planning grants and contracts at four academic health centers; four additional awards were made a year later. Experimentation is now going on and several models will be implemented in the next few years.

NLM, in collaboration with the National Institutes of Health Division of Research Resources, has supported research in medical informatics to make possible the rapid application at the bedside of the advances in medicine resulting from research. Now, at a rapidly increasing rate, the view of biology is shifting to the molecular structure of genes and their protein products. Research in the life sciences is becoming increasingly dependent on tools to store and manipulate large amounts of data on the behavior and structure of macromolecules. The ability to measure and change events occurring on a molecular level is particularly significant where the development of techniques to sequence, clone and remodel genetic material is leading to the control of life processes with a precision never before known. The continued pursuit of this knowledge is as much an information-processing problem as it is a problem in biology. Unfortunately, the institutional infrastructure for the support of the information-processing part of these endeavors is far less defined and developed than that for the biology. NLM already plays a crucial role in its bibliographic control of the published literature. The management of the rapidly emerging banks of data needs now to be organized and integrated.

With such important issues facing it, the NLM is now engaged in a careful look to the future. The initial phase of a long-range planning activity has just been completed in which NLM has had the views and advice of five panels of distinguished outside experts. The topic, "Research in Medical Informatics," was carefully and specifically considered by one of the panels.

The final recommendations of the overall panel are now under review by our board of regents. It is already clear, however, that the board readily accepts the importance of automated information systems and knowledge bases in its vision of the future and that research in medical informatics is critical in assuring the best of these future developments.

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Clinical Information Systems—A Review

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Two hypotheses are offered in this review of clinical information systems: that the technology is mature, and that benefits to patient care can be shown. More than ten years of operational experience exist with each general class of clinical information systems, and these systems favorably affect staff, reduce errors, improve accessibility to medical information and provide alerts and reminders. To reinforce the maturity hypothesis, most cited studies are also a decade old. Clinically oriented systems are practical and can improve the health care process—a key goal in this era of prepaid or prospective payment for services.

(Blum BI: Clinical information systems—A review, *In* Medical informatics [Special Issue]. West J Med 1986 Dec; 145:791-797)

Clinical information systems are defined as computer-supported applications with a relatively large and long-term data base containing clinical data that are used to assist in the management of patient care. Most hospital information systems are clinical information systems by this definition. Examples of systems that are not include a hospital billing system (no clinical data), a physiological monitoring system (no long-term data base) and a registry or research data-base system (not used in patient care). The technology for these systems is mature and their benefits have been shown.[1,2] Consequently, one should expect to find more widespread use of these systems in the coming decades.

As the name implies, a clinical information system is an application of information system technology. Like every tool-based product, the power of the clinical information system has been limited by the resources of the equipment available to support it. Consequently, in the early days of computing, clinical information system applications were speculative and experimental. In the late 1960s, large disk memories, data-base management systems and lower cost minicomputers made it possible to develop and evaluate operational systems. In the present period of relatively inexpensive equipment and widespread computer literacy, we are witnessing the general use of information systems in both clinical and health-administration applications.

The status of the clinical information systems is best understood when seen in the context of the medical informatics applications. We begin by identifying the types of objects processed:

- *Data.* These are the uninterpreted items given to an analyst or problem solver, such as the signals processed by an electrocardiograph or an imaging device.
- *Information.* This is a collection of data elements organized (or interpreted) to convey meaning to the user, such as an automated medical record or a flow sheet.
- *Knowledge.* This is the formalization of the relationships, experience, rules and so forth by which information is formed from data, such as signal-processing algorithms and the knowledge bases of expert systems.

This categorization of processed objects is artificial; there are no clear boundaries among the three. Nevertheless, there is a progression in complexity from data to information to knowledge.

Because of this increase in complexity, the first applications addressed only the least complex objects. We began with data processing, and now we are experimenting with the processing of knowledge. This is shown in Figure 1, which characterizes the applications by type and decade. It should be noted that there is a progression from concept to research to prototypes and, finally, to mature products. We have the greatest experience with data processing, which is now in its second generation of advanced development and is firmly rooted in the domain of biomedical engineering. Information applications went through a prototype period in the 1970s and are now mature. Finally, prototypes of the knowledge applications—decision making, expert systems and intelligent systems—are currently being evaluated in clinical settings.

While emphasis on knowledge processing is growing, the dividing lines between traditional information and knowledge-based paradigms—that is, data-base technology and artificial intelligence—are blurring. As will be pointed out, many clinical information systems rely on the application of medical knowledge. Moreover, one can expect this orientation toward integrating these paradigms to continue.

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ABBREVIATIONS USED IN TEXT

AAMRS = automated ambulatory medical record system
COSTAR = Computer Stored Ambulatory Record System
HIS = hospital information system
OCIS = [The Johns Hopkins University] Oncology Clinical Information System
RMRS = Reigenstrief Medical Record System
SMAC = Sequential Multiple Analysis-plus Computer
TMIS = Technicon Medical Information System
TMR = The Medical Record

System Models

There are two basic models for clinical information systems. The first is for hospitals, where the assumption is that there will be a limited number of patients, each treated for a relatively long period of time and each requiring a great deal of clinical information related to the current admission. The facility is large, has a number of separate departments and requires a large staff. In addition to the functions of health care delivery, there are also hotel functions, business-office functions, personnel functions and the like.

The second system model is for ambulatory care settings, such as health maintenance organizations and office practices. In these settings there are more patients, a need for long-term follow-up, relatively short-term episodes of illness with limited clinical data for each episode and few functions not directly associated with the provision of health care. Unlike the hospital setting in which the charge for the record-keeping function is small when compared with the other costs of care, information-processing costs in an ambulatory care facility are highly visible.

Applications	1950s	1960s	1970s	1980s
Data	Research	Prototypes	Mature	Refinement
Information	Concepts	Research	Prototypes	Mature
Knowledge	Concepts	Concepts	Research	Prototypes

Figure 1.—Scope of medical computing.

Consequently, the two general types of clinical information systems are very different in character. The early hospital information systems (HISs) were targeted to reduce labor costs. It had been shown that approximately a fourth of the labor cost in a hospital was associated with information processing.[3] It was speculated, therefore, that if some of this processing could be automated, labor costs could be reduced. Thus, the basic HIS model became one of linking the various users of information to reduce redundancy and improve transmission. As will be shown in the following section, this approach had only a limited impact on labor costs. But it did reduce errors, speed communication and facilitate medical decision making.

Figure 2 shows a block diagram of an HIS, emphasizing its communication role. At the center of the system is the nursing unit where all patient care is coordinated. Administrative and business functions are shown to the left, ancillary services to the right. Each is viewed as a "source" or "sink" for patient data in this diagram. Each hospital department, however, could redraw this diagram to make its functions the key operation. For example, the pharmacy's view of an HIS is that it is a collection of programs that supports the operation of the pharmacy: maintaining profiles, printing work lists, producing labels, reporting activities and recording charges. To the pharmacy, drug orders are inputs to be processed and the drug profile is part of their data base. To nursing stations, on the other hand, the order is a request for drugs and the profile is part of the medical record. Thus, an HIS is a large and complex system that must support many users with different perspectives. That is why it typically takes from six months to two years to install—even when no programming is required.

An ambulatory care system is considerably less complex. Figure 3 shows a model for the flow within an automated ambulatory medical record system (AAMRS). The central event is the encounter (patient visit). Some form of medical record must be available to the provider (physician) before the encounter. In situations where a patient comes by appoint-

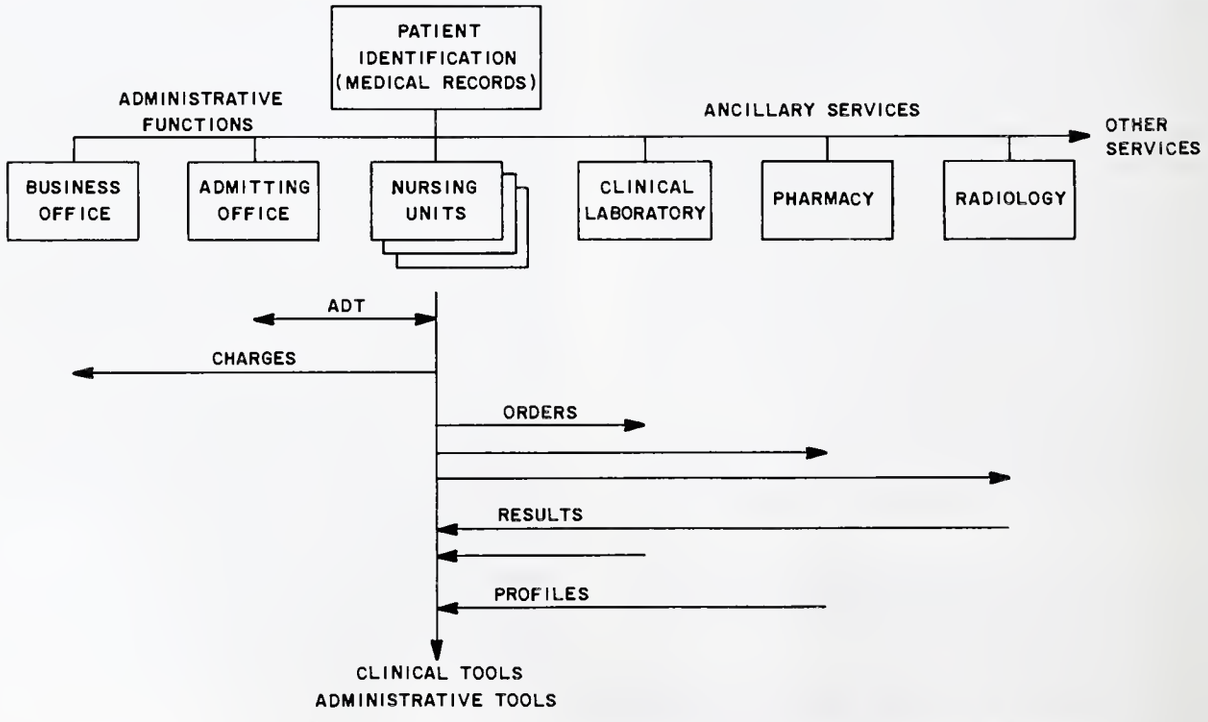

Figure 2.—Flow model of a hospital information system. ADT = admission, discharge and transfer

ment, an encounter form will be printed before the appointment date. The encounter form (for an AAMRS) typically contains some extract of the automated medical record plus space to record information derived from the current visit. The form normally serves as the permanent medical record, a data-entry form for the automated ambulatory medical record and a form for ordering follow-up actions and tests. In situations where a patient has no appointment, the encounter form may be printed on demand.

Within these two general models there are many variations. The orientation of the system may be to support administrative functions; the use of the system for patient care is seen, therefore, as fortuitousness. Conversely, the goal of the system may have been to support the patient care process. Systems with this objective also will be able by necessity to support almost all of the administrative and business functions; they must know where a patient is, what tests were ordered and drugs prescribed, what appointments have been made and kept and so forth. As a generalization, we note that systems designed for administrative purposes have difficulty adding clinical functions, but the reverse is not the case.

A second variation in clinical information systems is their scope of coverage. This is most pronounced in an HIS. In some cases, the HIS is limited to the basic admission, discharge and transfer functions plus one or more ancillary services. That is, the implementation approach is evolutionary: develop tools for one or more departments, learn from this

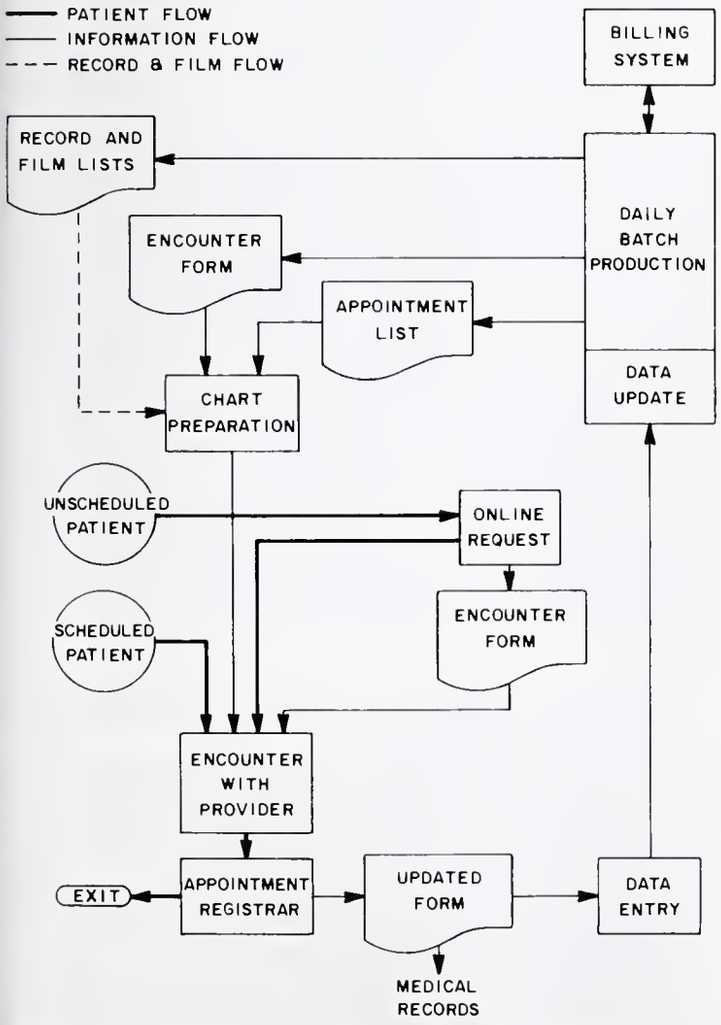

Figure 3.—Flow model of an automated ambulatory medical record system.

experience and add another department. With the growing availability of local area networks and stand-alone ancillary systems, there is a renewed interest in this approach. The alternative method—the holistic approach—seeks to implement all functions at one time. Because the risk generally is low and inasmuch as communication benefits increase with the number of communicating functions, there are many reasons to select this implementation path.

Some Hospital Information Systems

The following are HISs that have played an important role during the prototype evaluation period of the 1970s:

- The Technicon Medical Information System (TMIS) was installed at El Camino Hospital (Columbus, Ohio). It is one of the first HISs to be installed and was the subject of several major studies regarding the impact of an HIS.[4,5] The TMIS is an example of a holistic system designed primarily for administrative support. It has been in continuous use for more than 15 years and has been installed in 50 hospitals.
- The Problem Oriented Medical Information System, implemented by Weed and colleagues at the University of Vermont (Burlington), provides a completely automated medical record using a problem-oriented structure. The frames used by a provider represented a structuring of medical knowledge and a framework for organizing care.[6] This example of a care-oriented, holistic system is no longer in use at its prototype site; a commercial adaptation is available.
- The HELP system, developed by Warner and associates at the Latter-Day Saints Hospital in Salt Lake City, grew out of research in the early 1960s regarding the use of computers in patient care. The system was first implemented in intensive care units and then expanded to the rest of the hospital and its ancillary units. Medical knowledge is formalized as "HELP sectors," and the screening of all orders is invoked automatically. This is an example of a holistic HIS, designed to aid in patient care, that integrates both information and knowledge processing.[7,8] The system has been in continuous operation since the mid-1970s, and a commercial version is being evaluated.
- The Johns Hopkins University Oncology Clinical Information System (OCIS) was implemented by Lenhard and Blum and associates for a comprehensive cancer center. Although this is not a hospital information system, it is an example of how an information system can support patient care in a tertiary care setting. This system integrates inpatient and outpatient data, produces protocol-directed care plans for all inpatients and supports specialized functions such as blood product management and human leukocyte antigen type matching. It was implemented using only patient care resources and has been in continuous operation since the late 1970s.[9,10] Portions of the system have been transported to other centers.

This list of HISs emphasizes systems that have in some way contributed to our knowledge of clinical information systems. Naturally, there are commercial systems that use the results of the research and development characterized by the examples in this list. All of these systems—except the last—were recipients of significant external support. Thus, they were viewed, in part, as research activities. The OCIS, however, was started in 1975 and has been supported entirely by patient care funds. This may be taken as a sign of the field's

maturity: by the mid-1970s the available experience and technology suggested that the cost of a system could be justified solely on the basis of the anticipated benefits. Yet, readers should not be misled by the bias of this list; most HISs are implemented for administrative gains and cost reduction; few have a medical decision-making orientation.

Some Ambulatory Care Systems

Two events help in the cataloguing of AAMRSs. The first is a 1975 state-of-the-art survey conducted by Henley and Wiederhold in which they identified 200 potential systems.[11] On further examination, many of these were found to be no longer operating. From this list, 17 systems were selected for more detailed study. By the time the report was issued, one of these was also no longer in existence. The second event was a follow-up to this study in 1981.[12] Although most of the initial systems were still operating, in all but three cases their role in clinical care had remained the same or had contracted. The three clinically oriented systems reported on are as follows:

- Computer Stored Ambulatory Record System (COSTAR), developed by Barnett and co-workers at Harvard University, supports a completely automated medical record. Initially designed for a health maintenance organization, the system was rewritten in the late 1970s as a public domain version (COSTAR V), and assistance was given to small companies to integrate and maintain support to health care organizations. The system provides a billing system, appointment system and query functions as well as an automated medical record.[13,14] There are many COSTAR implementations throughout the world in facilities ranging in size from a hospital to a private practice.
- Regenstrief Medical Record System (RMRS), implemented by McDonald and co-workers at the University of Indiana (Indianapolis), was one of the first to build a medical knowledge base to produce reminders regarding therapy and tests. In preparation for each encounter, its knowledge is queried and the encounter form is modified to collect data appropriate to each specific patient; a list of reminders is also printed.[15,16] The system has been successfully transported to other facilities.
- The Medical Record (TMR) was developed by Hammond, Stead and their associates at Duke University (Durham, NC). TMR is an outgrowth of earlier work and is intended to provide a set of integrated tools flexible enough to meet the needs of both an office practice and a research institution.[17,18] The system is in use in practices throughout the country.

As in the list of HISs, this list of AAMRSs is short and biased by an interest in research rather than commercialization. Clearly there are more clinical information systems designed for ambulatory care settings; there are even more systems that provide only administrative support. Yet, as the two AAMRS studies suggest, a discouragingly small portion of the systems is designed to assist in patient care.

Maturity of the Technology

In the opening paragraph of this paper, my theses were stated: clinical information systems are mature and their benefits have been demonstrated. In this section we have identified systems that have been in operation for ten or more years—a clear demonstration of the technology's maturity. In the following section, the impact of these systems on health care will be examined.

Evaluation

The evaluation of a health care system generally is presented in terms of its structure, process or outcome benefits and its effect on costs. In the case of computer technology, it is also possible to view the impact of a system in terms of its enabling benefit—that is, the availability of the system enables an organization to carry out activities that would not otherwise be possible. The most dramatic illustration of this was seen in clinical laboratories when automated analyzers were introduced. For example, the Mount Sinai Hospital in New York did 260,000 tests in the entire year of 1965; once a Sequential Multiple Analysis-plus Computer (SMAC) was installed, the chemistry department was doing 8,000 to 10,000 tests per day.[19] This ability of a laboratory to do more tests, at a lower cost per test, with more rapid reporting removed some constraints on test ordering.

In the clinical laboratory, the use of computers enabled clinicians to order tests as necessary. In effect, the computer allowed clinicians to use familiar tools and techniques while suppressing the limitations of scale. That is, the computer system facilitated operations that would not be practical using manual methods. This is quite different from the contribution of the new imaging tools that began with computed tomography. In this case, a new technology was introduced, alternative diagnostic methods became available and the domains of efficacy could be established.

With clinical information systems, a great deal of the benefit comes from their enabling power. Reliance on the new tools tends to be gradual, the changes (and benefits) are perceived as minor and (often) the system is appreciated only during periods of failure. Thus, the benefits of clinical information systems are difficult to identify and evaluate. In many cases, their availability has led to the assumption of obligations that might not otherwise have been accepted. For example, the power of the HIS business systems has allowed hospitals to respond to complex external reporting requirements. These requirements were not design goals for the system; rather they were obligations appended after the ability to meet these needs was available. Thus, the HIS business system enabled expanded reporting. As will be shown in the next section, clinical information systems produce improvements in health care. Given their enabling power, if the resources are managed properly, then one should expect even more widespread clinical benefits to materialize.

Benefits

The benefits of a health care system are normally distributed among three categories:

- *Structure.*—The capacity of the facilities and the capacity and qualification of the personnel and organization.
- *Process.*—The changes in the volume, cost and appropriateness of activities.
- *Outcome.*—The change in health care status attributed to the object being evaluated.

What we have termed enabling effects are generally considered structural benefits. Most of the measurable effects of information systems, however, are seen as changes in the process. It is assumed that the changes in process will im-

prove the health care status, but to date there are no studies that clearly show an outcome benefit. In what follows, we summarize the results of some of the earlier studies relating to the process benefits. Note that most of these results have been available for a decade.

Impact on staff. The studies on the impact on staff may be divided into two categories. The first involves early implementations during a period when the use of interactive computing was relatively rare. The second involves studies during the current period of general computer familiarity. In the case of the TMIS at the El Camino Hospital, a mid-1970s study showed that nursing acceptance was always high.[20] In June 1974, 92% of the nurses favored the system. In part this reflected the fact that with fewer clerical requirements, more nursing hours became available for patient care. Similar acceptance of the HIS was found in the ancillary service departments. For these reasons, the availability of an HIS now is seen as an advantage in recruiting staff.

Acceptance by physicians has always been less enthusiastic. In the June 1974 El Camino Hospital survey, only 61% of the physicians voted to retain or extend the systems, and some of these still expressed negative opinions. In part, this limited acceptance stems from the facts that the system does not satisfy existing physician needs, their use may seem awkward,[21] the use of the technology may seem foreign to established physicians[22] and the acceptance of enabling technology occurs gradually over time. These issues of adaptation, diffusion and utilization are being restudied with the current generation of systems.[23] Acceptance of and familiarity with the technology seem to go hand in hand. Also, there is a tendency to accept a tool more readily when the user has participated in its design.[12]

Access to medical information. Because all clinical information systems maintain some form of patient record, they also will have some effect on the availability and structure of the medical record. In an HIS that contains subsystems for the ancillary services, for example, there will be more rapid reporting of results. As soon as a result is available, it is available to all authorized users. In addition to the advantages of more timely reporting, there also is the ability to organize the information to meet special needs. TMIS, like most HISs, allows analysts to structure the information produced—outputs—for use by different classes of user or department. COSTAR has specialized reports for pediatric, hypertensive and other patient categories. RMRS modifies the flow sheets and encounter forms to fit the patient problem list and OCIS routinely plots patient functions according to physician-established formats for disease and therapy combinations. Thus, the medical record is viewed as a ubiquitous, dynamic source of information rather than a physical sequential document.

The fact that medical records may be referenced concurrently from many different locations improves their availability. Records no longer are "lost"—a major impediment to care in situations where there can be emergency admissions (such as at an oncology center) or unscheduled visits (an emergency room). For example, the "core" record was designed for outpatient departments in a large teaching hospital where locating the paper record was not always easy. One short evaluation of an earlier version of the system found that 17% of the patients in a medical clinic had no charts available on the day before an appointment and 10% had no charts available at the time of a visit. In contrast, 95% of all patients had a printed automated record in time for a visit.[24] Similar results have been reported elsewhere.

Given the fact that an automated record can always be found, the next question is to determine what information is actually used. In one interesting study in an ambulatory care setting, providers were divided into two groups. The first group received a manually maintained flow sheet plus the complete record; the second group received only the flow sheet but was allowed to request the chart as well. At the end of each encounter, a physician reviewed all charts for overlooked clinical information. In all, 59% of the study group physicians (flow sheet only) chose not to receive the full record. Moreover, the study group was found not to differ from the control group with regard to following up clinical information as measured by the chart reviews before and after patient visits. The investigators concluded "that a flow-sheet type of summary medical record can serve as the sole source of clinical information in a substantial number of outpatient follow-up encounters in a medical subspecialty clinic without deterioration in the communication of clinical information."[25]

Thus, it is clear that the availability of automated records enables information that contributes most to the decision-making process to be extracted and formatted. Such formats should improve the recognition of trends, reduce information overload and foster better patient care.

Reduction in errors. Computer-stored medical data should be freer from errors than the traditional manually recorded record. A computer can be programmed to reject unreasonable values, integrating information reduces transcription errors and the ability to present the same datum in a variety of contexts facilitates the recognition of erroneous values. This has been confirmed in many studies. It will suffice to report on the mid-1970s work of Simborg and co-workers.

In a ward-management system that processed orders, Simborg and colleagues compared automated and unautomated units and found that with automation transcription errors were reduced (1.7% for the automated unit as compared with 7.3% for the control). They also recorded a lower rate for failure to carry out an order exactly (5.8% versus 14.7%).[26] Comparing an automated unit dose and unautomated bulk-distribution pharmacy system showed similar results. Errors of commission in the manual system were 4.6 times more frequent.[27] Although the technology used for these early systems has rendered them obsolete, they represent some of the earliest demonstrations of the ability of an HIS to reduce errors.

Surveillance and reminders. If the mere use of a clinical information system to store and display patient data facilitates understanding and reduces errors, then what can be accomplished if the processing is augmented by the application of medical knowledge?* First, knowledge may be applied in one of several basic ways. All actions may be evaluated against some knowledge base so that alerts can be issued if potentially dangerous patterns are identified. Most drug-drug interaction facilities operate in this way. Second, the knowledge may be used to suggest therapies or tests based on standard treatment algorithms and patient status. Reminder and protocol-di-

*We use the term medical knowledge in its generic sense as opposed to implying that it is structured as a knowledge base to be accessed by an artificial intelligence application.

rected care applications are examples of this mode. Finally, a third mode of application is consulting a system for expert advice or critiquing—most artificial intelligence systems fall into this category.[28]

By way of an example of the surveillance approach, the HELP system maintains medical knowledge and examines all orders with respect to these established criteria. In a 1976 report it was shown that of more than 13,000 patients monitored, 5% of the patients' pharmacy orders indicated some form of drug-drug interaction and initiated an alert, and 77% of these alerts resulted in changes in orders.[29] A more recent study at Latter-Day Saints Hospital (1981 to 1982) found that 1.8% of patients generated a pharmacy alert that was considered life-threatening and that there was a 94% physician compliance to the life-threatening alerts.[10]

RMRS, as previously noted, produces reminders for each visit. McDonald has studied the impact of these reminders on physician behavior. The first of these studies was published in 1976.[30] Because RMRS maintained a complete data base, it was possible to identify what actions were taken during an encounter, such as ordering a test or prescribing a medication. Thus, there was an environment to determine if the actions of a clinician differed when reminders were presented. Over a period of eight months, some 600 patient visits were assigned to a control and a study group. Only the study group received the reminders. For both groups, however, the reminder suggestions and the encounter actions were recorded. The results indicated that when reminders were present, there was a greater tendency to follow their advice. This was most dramatically noted in the case of clinically significant changes in therapeutics, where the responses were 47% with and 4% without computer assistance.

In this evaluation, the patients were assigned to the study or control group; few patients had the same provider in successive visits. McDonald next asked the question, What if there was continuity of care and the clinicians were assigned to study and control groups: could the reminder system be used as a "training" tool to "perfect" the physicians' performance? A crossover study was designed with two groups of physicians. One group spent seven weeks with the reminders and then nine weeks without them; the other group spent the first seven weeks without reminders and the final nine weeks with them. All groups using the reminders were asked to comment on them and indicate if they agreed or disagreed with the protocol or if there were insufficient data to determine if the protocol applied to a given patient. As in the previous study, the response to events was greater when reminders were present.

It was expected that the reminders might alter behavior. There was no difference, however, in the behavior of the two groups during the control period. That is, there was no residual change in performance (no training effect) for the group that initially used the reminders. Moreover, when one divided the physicians by level of training, one could find no significant overall effect on the results. This led McDonald to conclude that the problem was not one of training; rather, he said, "it is very likely that the physicians in these studies were simply unable to detect all the multitudinous conditions specified by the standards used."[31] He called this phenomenon information overload.

The ability to provide reminders or guidance also has been shown with other systems. COSTAR has been used to verify that follow-up actions have been taken in the event of a positive throat culture.[32] Wirtschafter and associates have shown how algorithms can be used to guide outreach physicians in administering cancer chemotherapy. In one study they reported that protocol compliance was 94% for the group using the system and only 64% for the nonuser group.[33] Thus, even before we begin to exploit the new tools that research in artificial intelligence is producing, there is ample evidence to suggest that we are barely taking advantage of the things that we already know how to do.

Costs. The initial goal of the HIS was to reduce labor and its associated costs. Clearly, equipment costs have fallen dramatically since the 1970s, and functions that were not cost effective at that time may be so today. Nevertheless, it is useful to stop and consider what is known about the effect of clinical information systems on cost.

In 1981 Drazen and Metzger reviewed ten cost studies of automated hospital information systems and reported the following conclusions[34]:

- Few rigorous studies have been conducted of the cost effects of implementing automated hospital information systems.
- Most of the work done in this area in the past has involved predicting cost impacts. Somewhat overstated cost savings—largely the result of unrealistic labor savings and the inclusion of revenue effects—and understated system costs may have produced unrealistic estimates of the net cost impacts of an automated HIS.
- Little work has been done validating the results of predictive methods. Therefore, there is very little documentation of the actual impact of an automated HIS on the productivity of hospital staff or on overall changes to guide the conduct of cost assessments.
- Through improvements in information flow, an automated HIS offers benefits to the quality of service, and these are usually major motivations for a hospital to implement a system. More exploration needs to be done of the cost implications of improvements in the quality of service, such as improved turnaround time for test results reporting and a decreased loss of information.
- Revenue recovery for charge capture is not a measure of changes in the cost of operating a hospital and, therefore, should not be counted among the cost effects.
- Cost studies have been conducted for different hospital settings and system configurations. The specific methods used are generally applicable, however, to any setting or system type. The purpose in undertaking the cost study determines the approach that is used.

As these conclusions suggest, most cost studies are prepared to justify a purchase and are never evaluated. The reason for this is that evaluating an operational system is both difficult and expensive. For example, consider the experience of the El Camino HIS evaluation. Work began in the early 1970s, the data were collected in the mid-1970s and the last report was issued in 1980. Clearly, over this period of time there were many changes in the El Camino Hospital, the national health care system and computer technology. The conclusions of the final report were as follows:

The results indicate that the system improved productivity in the medical care departments and caused an overall reduction in patient length-of-stay. From a

total hospital cost perspective, however, the results were not definitive. Under the assumption that support department cost increases that were found were not directly caused by TMIS, the system was estimated to be approximately 60 percent self-supporting in 1975.[20]

Read another way, this means that 40% of the system's operational cost produced the benefits cited in the first sentence.

Perhaps the proper conclusion to draw from our studies of the cost impact is that major reductions in operating costs do not seem to result from installing a clinical information system. The major gain is in the benefit to patient care and the enabling of new tools that improve care. In the previous era of cost reimbursement, savings in labor could be transferred to increased profits. But in an environment of prepaid health care and prospective payment for hospital admissions, improved health care becomes the avenue to profitability. And it is here that clinical information systems have shown their efficacy.

Summary

I began by stating a hypothesis that should now be accepted as valid: clinical information systems represent a mature technology of demonstrated benefit. When we consider how few systems have been deployed, however, we must wonder what is necessary for the successful transfer of this technology. I propose the following areas for further activity:

- Education is required so that clinical users will understand what already is known. This will enable them to build on the state of the art rather than to reimplement it. It also will produce a demand for more sophisticated products that should act as an incentive to commercial vendors. Fortunately, a new generation of texts is available to aid in this education process.[1,35]

- Research is necessary in two major areas. First, the impact of clinical information systems on the health care process must be evaluated. Some studies have been briefly examined here, but much folklore lingers. Second, the clinical information systems should be viewed as a data repository to be referenced by knowledge-oriented tools. This implies research topics in knowledge representation, communications, human factors and the like.

- Commercial products that take advantage of our deeper understanding are needed. There is a dilemma for commercial vendors. Users expect tested, robust systems, and this generally takes five years from concept to operation. On the other hand, users also want the latest features. This conflicts with the economics of development. If the marketplace demand is sufficient, however, vendors may be encouraged to use the new generation of software tools to build knowledge-oriented systems.

By way of conclusion, I see the previous decade as one of discovery and validation. I would hope that the next will be characterized by the exploitation of previous developments and the integration of existing systems with medical knowledge and knowledge-based paradigms. If this occurs, then there is the possibility that clinical information systems will have an impact on health care delivery systems in the 1990s similar to that of the SMAC on the clinical laboratories in the 1960s or computed tomography on the diagnostic tools of the 1970s.

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ARAMIS (The American Rheumatism Association Medical Information System)

A Prototypical National Chronic-Disease Data Bank

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ARAMIS is a prototype of a national chronic-disease data-bank system consisting of parallel, longitudinal, clinical data sets from 17 diverse locations; the data describe the courses of thousands of patients with rheumatic disease followed over many years. Chronic-disease data-bank systems include the data themselves, protocols to ensure their quality, computer systems for their manipulation, statistical procedures for analysis and an appropriately skilled staff. Such a data resource facilitates analyzing long-term health outcomes and the factors associated with particular outcomes. Such systems are mandated by the overwhelming prevalence of chronic illness; the variability, complexity and uniqueness of a patient's course; the difficulties of traditional randomized approaches in these areas, and the time span required for studying these problems.

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ARAMIS (the American Rheumatism Association Medical Information System) is based on the premise that many of the most important problems of contemporary clinical medicine require data banks of chronic diseases for their solution. ARAMIS is one such data bank, containing detailed longitudinal patient information collected prospectively and carefully controlled for quality. Information is stored for thousands of patients and tens of thousands of patient-years of observation.[1,2] The system includes the data, the computer systems that allow efficient manipulation of data, a set of evolving investigational methods for approaching the study of such data sets and the appropriate staff to carry out the required activities.

In chronic-disease data-bank systems the complete courses of thousands of patients from different settings are stored on computers and through communication networks become accessible to investigators at many locations. Unlike clinical investigations based in the medical record room, data are collected with a prospective protocol using standard, defined observations. Patients are regularly followed even when they move or change physicians. Measurements include broad health and economic status indicators. In essence, each patient is on a universal prospective research protocol. In this review we present our personal view of the history of ARAMIS, the principles on which it is based and its accomplishments.

The Eight Principles of ARAMIS

The development of ARAMIS has been based on eight principles, discussed in more detail in a previous communication[3]; these principles support the premise with which we introduced this article.

1. *Because the purpose of the medical care system is to improve health outcomes, clinical investigation must include measuring these outcomes.*

A medical care system exists to minimize death rates, to decrease disability, to reduce discomfort, to minimize the drug and therapeutic toxicities of the care itself and to reduce the economic impact of illness and its treatment. These five broad dimensions of health outcome—death, disability, discomfort, drug toxicity and dollar costs—have now been shown to be measurable, relevant and surprisingly discrete.[3] Such measures, rather than merely "process" measures such as antibody levels or sedimentation rate, should serve as the major dependent variables for study.[4,5]

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ABBREVIATIONS USED IN TEXT

ARA = American Rheumatism Association
ARAMIS = ARA Medical Information System
MRFIT = Multiple Risk Factor Intervention Trial
TOD = Time-Oriented Data Base

2. *Chronic diseases now constitute the major national illness burden.*

Over recent decades, the national burden of illness has shifted strikingly from acute infectious disease to chronic illness.[6] Currently the major medical problems in developed nations are atherosclerosis, cancer, arthritis, emphysema, cirrhosis, other chronic diseases and trauma. Chronic diseases at present cause more than 80% of the national mortality and morbidity.[6,7] These illnesses are characterized by slow development, insidious progression, widely varying patient courses and multiple interactions over time with various environmental and medical determinants.[8]

3. *Studies of health outcomes, therefore, require long-term longitudinal studies.*

Variables that are predictive of eventual patient outcome in cases of chronic illness predate the outcomes themselves by many years. Patients with arthritis, for example, are typically treated with a score of different medications by 15 or 20 physicians over a quarter of a century. The effects, good and ill, of treatment programs accumulate over time, and treatment involves many different modalities applied sequentially and concurrently over a period of many years. In such a complex situation, definitive studies require a large number of patients observed for long periods of time. Expensive experimental studies, as with the Multiple Risk Factor Intervention Trial (MRFIT) study,[9] address only a single major question and are thus seldom feasible. Prospective observational studies, therefore, must represent a major approach to the study of chronic disease.

4. *The effective study of long-term outcomes must be systematic.*

A traditional research cycle consists of developing a hypothesis, carrying out an investigation, analyzing the results, forming conclusions and formulating a new hypothesis for subsequent study. With long-term questions, however, the duration of the cycle does not permit the efficient accumulation of knowledge by this approach. One cannot wait for results from one study to be completed before beginning another. A new strategy is needed in which an underlying system allows new data to be collected and new studies to be introduced as soon as a new question arises—and thus for multiple studies to be done simultaneously. A feedback loop is required in which the data being systematically collected gradually evolve in nature as previous results and the emerging new questions lead to increased understanding of future data requirements.[10]

5. *Studying long-term health outcomes requires developing and using new observational analytic techniques.*

Traditional human experimentation, with randomly selected treatment and control groups, often is effective and practical for short-term questions. For long-term studies, however, it is seldom ethical or possible to assign persons to one or another group for life. With time and with many secular influences, the number of dropouts in both treatment and control groups increases to the point where conclusive analysis is no longer possible. The cost is prohibitive, even for medium-term studies. Very expensive studies—such as MRFIT at $115,000,000—have yielded inconclusive results, and no new experiments of this size have been funded in recent years.[9]

Observational studies, on the other hand, are often justifiably criticized for not being true experiments. Good observational study methods, however, can minimize many of the problems. Data-bank systems permit studies to be protocol-driven and prospective, with data collected "blind" (study hypothesis unknown to observer) and of a quality equivalent to that of randomized experiments. Moreover, statistical techniques of analyzing by strata, using several control groups, carefully adjusting for differences between study groups and using matched controls may minimize the difficulties of observational studies.

6. *Long-term data must be collected for more than one purpose.*

The long time and great expense required to undertake long-term studies of chronic diseases necessitate that the collecting of multipurpose data be economically justifiable. The same basic data can support many current and future studies unthought of when the data were initially collected.[3]

7. *The "real world" contains multifactorial influences on outcome.*

The outcome of chronic diseases is influenced by social and economic considerations, patient compliance with therapy and complicated interrelationships among medical treatment, surgical treatment and various other factors. Meaningful analysis of chronic-disease outcome requires a more complicated biologic, psychological and social model of disease, the study of a larger number of patients and the development of new techniques to deal with the complexity. The classic "reductionist" scientific experiment can examine only a small, tightly defined portion of such a complex disease model and thus cannot account adequately for such complex relationships.

8. *Prospective protocol-driven data are required.*

In our view, these principles mandate the development of computer data-bank systems for chronic disease as a major approach to investigating human illness. They also serve to define the characteristics that such a system must have. There must be a large number of patients from diverse settings. Data collection must be standardized using rigorous prospectively applied protocols. Data must be collected serially and over the long term, with intensive efforts at quality control. Follow-up must be as complete as possible. Patients must be enrolled consecutively and the data to be collected must be regularly reevaluated. Reliable and valid measurements of outcome must be made and repeated. Sophisticated information management tools are required and access to the data by many investigators must be possible if many questions are to be addressed and the potential economies of scale realized. Statisticians must develop improved approaches to study design, analysis and interpretation.

On a practical basis, such data banks can be used in establishing a feedback loop between long-term outcome and antecedent factors, determining the natural history and prognostic

factors of illness and defining and classifying diseases. Clinical benefits include identifying subgroups of patients who have different outcomes and the risk factors for particular outcomes, analyzing the costs and benefits of different treatments and better delineating the productive and relatively nonproductive endeavors of medicine.[10]

The History of ARAMIS

Five general stages in the development of ARAMIS can be identified:

1. *Development of the Time-Oriented Medical Record*

Traditional medical records represent a nonsystematic approach to accumulating data that prevents combining data across patient cases without retrospectively abstracting sparse and nonstandard data at the time of a study. We developed the time-oriented record as a framework for systematically and prospectively collecting data that encouraged more complete data recording, with the additional hope that the chart format would assist clinicians in reviewing records efficiently and in determining the trends and the tempo of illness in an individual patient. The time-oriented chart displays clinical information on "flow sheets," with time represented on the horizontal axis (Figure 1) and the variables to be observed on the vertical axis. Time-oriented records are more formally structured than traditional records and are slightly more difficult to complete initially. But as a complex patient course evolves, they rapidly become more effective for reviewing many encounters and are thus easier to use than traditional formats.[11,12]

Many of the data-quality problems of clinical research are a result of incomplete physician observation and recording. The format of our original time-oriented records on rheumatic disease has evolved (through 13 revisions over the years) toward an increasingly "physician friendly" format, resulting in more complete recording of data. With our present records, time-oriented flow sheets are used for laboratory and therapeutic information, as well as other quantitative data, but a single-page form is used for qualitative clinical observations. Medical histories that are self-administered by patients and reviewed by a physician are used extensively.

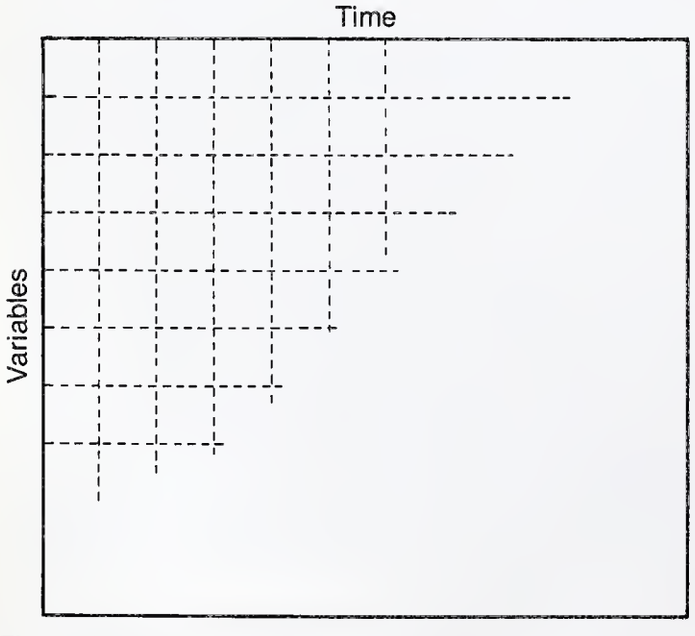

Figure 1.—Schematic representation of a time-oriented medical record.

2. *Development of the Uniform Data Base of Rheumatic Disease*

Data-bank projects in the rheumatic diseases developed nearly simultaneously at four institutions from 1966 to 1968. It soon became clear that each institution would become fixed to its own initial data set, precluding comparison or pooling of data, unless a common descriptive vocabulary could be negotiated. A computer committee of the American Rheumatism Association (ARA) was formed, and a conference involving 29 institutions was held resulting in the initial formulation of the Uniform Data Base of Rheumatic Disease. A common descriptive vocabulary was developed that lists 422 diagnostic, historical, physical examination, laboratory and therapeutic variables to be used, in whole or in part, by all institutions. Institutions were permitted to add variables of their own choosing. The uniform data base was designed to be revised periodically, which has occurred at about three-year intervals. There are now about 40 institutions using the uniform data base.[13]

Next, agreement was sought on the definitions of terms. The ARA Glossary Committee developed a dictionary of rheumatic diseases, which provides definitions and protocols for the data-base variables. Such definition is critical to improved precision in teaching and to the quality of clinical data. Volumes I and II of the dictionary have now been published.[14]

3. *Development of Time-Oriented Data-Base Management Systems (TOD and MEDLOG).*

A data bank[11] was conceived as a collection of individual time-oriented patient records that could be represented as a three-dimensional array (Figure 2). Thus, each data point had a unique address created by the specification of three coordinates. Computations along the time axis were facilitated by this organization. TOD (Time-Oriented Data Base) represents the original mainframe computer data-management system, and MEDLOG, developed by the Information Analysis Corporation with ARAMIS collaboration, is the currently available microprocessor system.[15,16] Both systems have closely comparable architecture.

Data are entered into a main file interactively from the patient record or from another computer through telephone lines, magnetic tape or floppy disk (Figure 3). During a following entry, a number of quality-control features are executed and errors corrected. Periodically, after additional data-quality checks, the file is transposed (inverted and ordered) into a second file, the transposed file, which is used for statistical analysis. The transposed file is not always current with data entry, but is always "clean" with regard to data quality for retrieval and provides a stable data set for analysis.

In the main file, a record consists of a patient visit: a string of numerical values describing the patient's status at that visit. In the transposed file, a record is a long, ordered string of values for a particular variable; these records often include 20,000 to 30,000 numbers. Analysis across patient data, the fundamental data-bank requirement, is facilitated by this file structure because it is no longer necessary to look through each patient record to find the data but only at the records pertaining to the variables of immediate interest.

Analysis programs begin by specifying a patient group (or subset) to be examined. A "patient subset" is a list of numbers that identify persons who fulfill particular criteria. These per-

sons may be specified by any combination of variables, using ranges of values or increases or decreases in value for a particular variable. All Boolean operations are supported. In contrast, a "visit subset" is a collection of only those specific visits at which particular criteria were met. Visit subsetting allows investigation of a particular portion of a patient's course and comparison with other portions of the same patient's course.

After specifying a subset, the user selects a particular retrieval program. These programs analyze data in a basic format, such as a histogram or a scattergram, but are otherwise entirely general; they will operate with any variable and any subset. Programs provide histograms, scatter plots, life-table analyses, comparison of means, comparison of proportions, multiple logistic regressions, multiple linear regression, recursive partitioning and contingency table analyses, among others. Programs also format the data for passage to the standard statistical packages of SAS (Statistical Analysis System), BMDP (Biomedical Data Programs) and SPSS (the Statistical Package for the Social Sciences).[2]

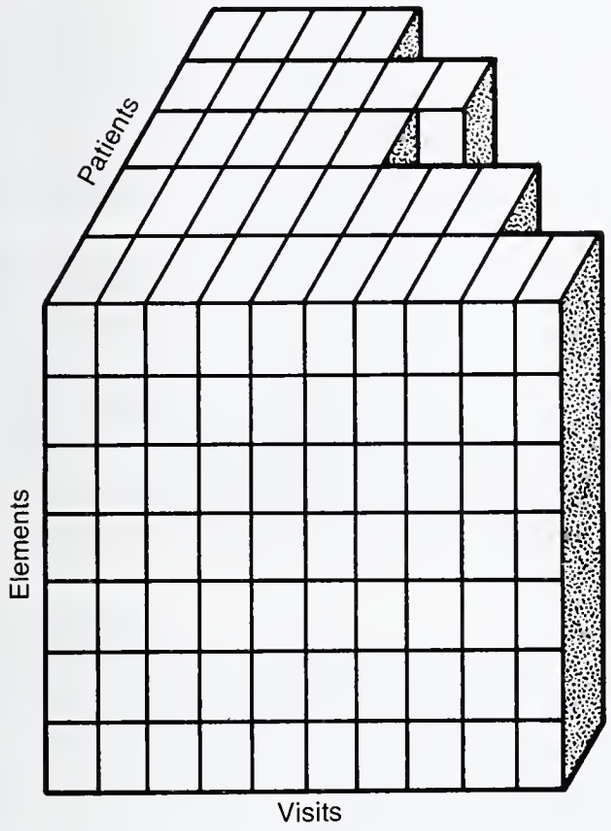

Figure 2.—Schematic representation of a time-oriented data bank.

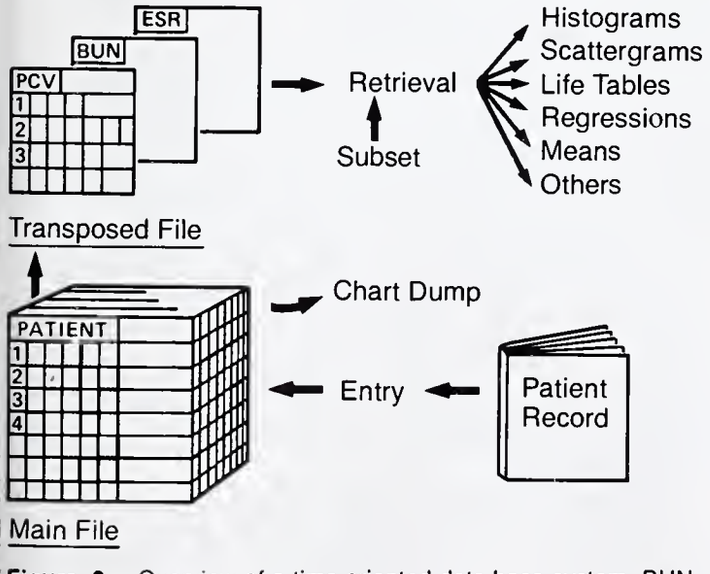

Figure 3.—Overview of a time-oriented data-base system. BUN = blood urea nitrogen, ESR = erythrocyte sedimentation rate, PCV = packed cell volume

The TOD system operates on the Stanford 370/3084A computer and is written in PL/1. MEDLOG is written for the IBM personal computer PC/XT and AT and is programmed in the languages PL/1, assembler and C.[15,16] Most operations, including data entry, are interactive. Microprocessor workstations are configured with 20 to 100 megabytes of additional hard-disk storage. The entire system currently contains about 300 megabytes of data. Data may be transferred between the mainframe and the microprocessor units.

4. *Development of a Pilot National Data Resource for Arthritis (ARAMIS)*

Conceptually, a national chronic-disease data-bank system is simply a collection of data banks with similar variables at different locations. A common schema (dictionary) defines the system and renders the different data banks compatible.

ARAMIS currently has 17 data banks in the United States and Canada. Responsibility for the integrity of data and for maintaining each data bank rests with the principal investigator of that data bank. Common data quality and follow-up protocols are used. Data quality is systematically reviewed by the ARAMIS core staff using audit procedures that compare patient chart data with information in the data bank.

Specific data banks have been selected for particular reasons; each consists of consecutive patient data with defined entry characteristics. One data bank may be strongest in longitudinal data for the disease systemic lupus erythematosus, another on rheumatoid arthritis. Some follow results for orthopedic procedures, and others trace the course of arthritis in children. Some represent urban centers, some tertiary care institutions and others (such as HANES I) represent population-based patient groups. While data are sometimes pooled between data banks, the strength of a system is in the ability to do parallel analyses in several settings and to confirm or contrast findings in different patient populations. ARAMIS currently contains information on more than 23,000 patients and 150,000 patient visits, covering more than 160,000 patient-years of experience, with some 60 million pieces of individual information.

The original configuration linked peripheral centers to the central computer by TYMNET and TELENET communication linkages, allowing access through telephones in the United States or Canada. This system remains in use for analyzing pooled data and for extensive computational tasks. In general, however, data are now entered into MEDLOG microprocessor data banks, and these data banks are then periodically transferred to a large computer over telephone lines or by mailed magnetic tapes. Information from a single data bank may be analyzed directly in MEDLOG or a microprocessor and additional data sets from other institutions may be installed on that microprocessor as well, if desired. The most time-consuming tasks, consisting of data entry and quality control, are thus now done in a distributed manner, with major savings in cost and efficiency.

A basic principle of ARAMIS is open, shared data. ARAMIS data are available to all qualified ARAMIS investigators. Potential projects are reviewed by a projects and publications committee where the study design is sharpened and possible conflicts anticipated. Patient confidentiality is absolutely maintained; identifying information about any patient within ARAMIS is available only to a physician responsible for a particular data bank.[10]

5. *Development of Outcome Measurement Techniques*

Originally, the uniform data base contained only traditional medical variables. It soon became apparent that data on socioeconomic and psychological variables were not adequate and that such variables were clearly important in studies of long-term outcome. Outcome itself was neither defined nor measured adequately. Accordingly, a major effort was applied to defining long-term patient outcome and developing methods for its measurement.[17-20] These measurement instruments (collectively referred to as the Health Assessment Questionnaire), focusing on disability, discomfort, iatrogenic effects, economic impact and mortality (Figure 4), have been developed, tested, revised, validated and widely used.[17-20]

Over the long term, the adequacy of patient follow-up becomes a central criterion of the quality of a system. Physicians' office records usually do not systematically follow patients when care is given elsewhere. Because patients with arthritis typically change physicians (and even eities) with some frequency, accumulating "dropout" percentages weaken study conclusions if patient follow-up has not been aggressively pursued. Developing instruments for measuring outcome, self-administered by patients, makes it possible to follow patients by mail or telephone. ARAMIS has moved toward a concept of a comprehensive visit for each patient each year at which outcome is measured, needed laboratory tests done and a particularly thorough physician assessment carried out. Questionnaire self-assessment is done each six months. The development of a medical record that serially displays overall health status information is felt critical to the clinical management of patients with chronic illness and thus a benefit to the recording physician and the patient.

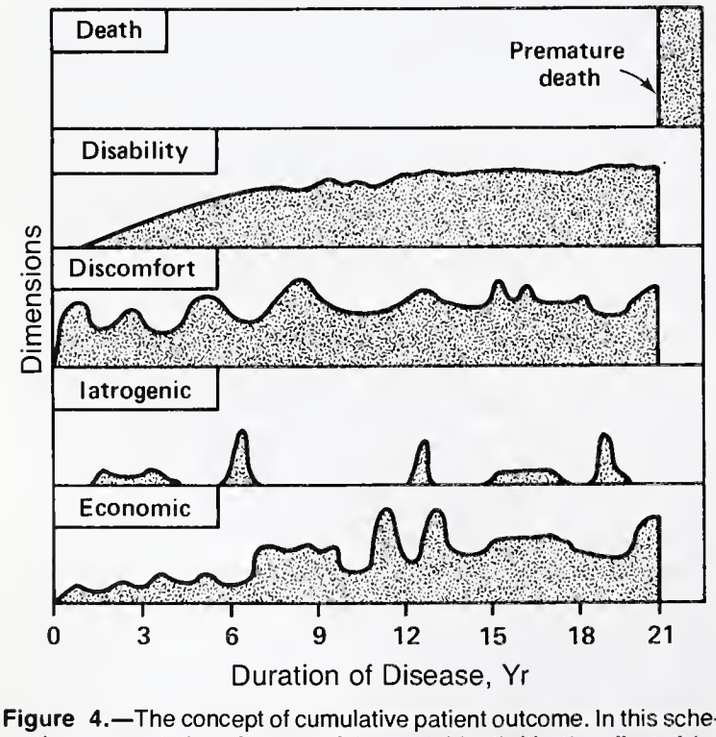

Figure 4.—The concept of cumulative patient outcome. In this schematic representation of a case of rheumatoid arthritis, the effect of the disease on each outcome dimension throughout the course is represented by the stippled areas.

Applications

ARAMIS has 45 associated investigators and about 100 projects under way at any one time; about 40 studies are published each year, and more than 250 ARAMIS publications have emerged to date. Some of these studies have concerned developing methods as described above. The time-oriented medical record,[1-3] the dictionary of rheumatic diseases,[14] documentation of time-oriented data-base software[11,12,15,16] and the development of particular statistical enhancements such as stepwise logistical regression have been described. The concepts of assessing outcome and developing instruments for measurement have been frequent topics.[17-20] More recently, methodologic papers describing postmarketing surveillance for drug toxicity and uses of recursive partitioning for patient stratification have been reported. Periodically, the entire system—its accomplishments and its current status—has been described.[3]

Clinical investigations have become increasingly formal. We have become skeptical of unadjusted tabulations of raw data beeause of the difficulty in definitive interpretation. Accordingly, ARAMIS has evolved a projects and publications committee that requires a formal investigative protocol before any investigation, review of the protocol and the proposed analysis at several steps by a committee experienced in biostatistical and methodologic evaluation and both internal and external review before publication in a peer-reviewed journal. The major information flow to clinicians is through the medical literature.

Clinical studies can be grouped into several general categories. First, defining the rheumatic diseases themselves has been an important activity. Studies have analyzed the criteria for classifying rheumatoid arthritis and have developed new criteria for juvenile arthritis, scleroderma, systemic lupus erythematosus and osteoarthritis of the knee. Currently under way are revisions of the rheumatoid arthritis criteria and studies of vasculitis and fibrositis. These studies have been done in collaboration with the criteria committee of the American Rheumatism Association.[21-23]

Second, ARAMIS has emphasized identifying subsets of patients within classic diagnostic entities. Such applications have been made in patients with juvenile rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, scleroderma and other conditions. For example, identifying the subset of "late-stage lupus nephropathy"[24] enabled hazardous therapy to be reduced in patients with systemic lupus who had uremia and encouraged the use of renal dialysis and renal transplantation in such patients. In cases of scleroderma renal crisis, successful medical management by aggressive antihypertensive treatment has followed from ARAMIS reporting of the management of the first three survivors of this dramatic syndrome.[25]

Third, many studies have had economic implications. The cost of different categories of disease, the variables predictive of high-cost patients, the identification of the most prevalent and the most expensive services and the effects of different treatment regimens on direct and indirect costs have been

subjects of study.[26,27] A more selective use of laboratory tests has been encouraged by an emphasis on laboratory variability and the marginal benefit of specific procedures.[28]

Fourth, studies of long-term outcome have analyzed the effects of initial variables on patient outcome after ten or more years. Outcome studies have explored mortality in cases of rheumatoid arthritis and systemic lupus, outcomes after total joint replacement and projected disability outcomes in rheumatoid arthritis and other disorders.[3,29,30]

Finally, therapeutic effects have been studied. These studies have been both observational and randomized in type, and both efficacy and toxicity have been described. Whereas ARAMIS is frequently associated with observational studies, trials that are "embedded"—prospective, randomized, double-blind and controlled—are frequently done, as with the use of nonsteroidal anti-inflammatory agents in rheumatoid arthritis, antihypertensive agents in scleroderma and cytotoxic agents in systemic lupus erythematosus.[3,31-34] Observational studies of cytotoxic treatment of systemic lupus, D-penicillamine therapy in scleroderma and others have been reported. The overall impact of therapeutic agents on costs, disability and symptom levels has been studied comparing the effects of commonly used antirheumatic agents.[31-35]

Therapeutic toxicity has been systematically studied by the development of a formal postmarketing surveillance system that serially records drug toxicity each six months. Data are collected in a protocol similar to that used in premarketing studies, which has allowed increased precision in comparing the side effects of different agents, delineating long-term side effects and noting the effects of concurrent factors such as age, race, sex and alcohol on side-effect rates.[3,36,37]

Future Evolution

We foresee that chronic-disease data-bank systems will continue to evolve toward distributed microprocessor networks with increased computational power available at work-stations. Soon to become available will be 32-bit microprocessor units with 1,000 megabytes of desktop data storage. The national arthritis data resource will increasingly evolve toward a series of carefully maintained meta-data banks aggregated from many sources with comprehensive data in particular areas, such as specific disease categories. Such data sets may be easily replicated and made available to investigators both within and outside of ARAMIS. Data acquisition, quality control, follow-up and outcome assessment, carried out centrally, will provide data of extraordinary usefulness. Compatible computer systems are being used increasingly in private practice settings, and larger amounts of data from more diverse clinical settings are becoming available.

Chronic-disease data banks begin to mature as the duration of follow-up approaches the average duration of the diseases under study. With time-oriented data, it becomes possible to examine the cumulative impact of a disease (the areas that are stippled on Figure 4), allowing more sophisticated analysis of the effects of treatment (and other variables) on the overall course of a disease rather than merely on the final status. The ability to compare the successive cohorts of new patients entered in the study each year from diverse centers will allow review of the changing characteristics of diseases, changing approaches to their treatment, changing determinants of cost and changes in outcome accruing to the successive cohorts.

Finally, a combination of the complementary attributes of "expert" systems using rule-based artificial intelligence techniques and the plentiful raw clinical data of chronic-disease data banks offers attractive conceptual opportunities. Rules may be developed by quantitatively analyzing actual experience rather than by armchair tactics, and the relationships between raw data such as "serum creatinine" and "proteinuria" and conceptual syndromes such as "active lupus nephritis" may be explicitly and rigorously defined.

The ability to summarize and display complex patient courses will improve the ability of physicians to effectively review the course of diseases as data-management systems become more compatible in individual clinical practice. Those involved in clinical research may combine effective patient management with the accumulation of valuable research data. Systematically assessing outcome in clinical practice will aid clinicians in appreciating the long-term course of patients with chronic illness.

In the past decade rapid progress has been made in hardware capability, in software support, in analytic techniques and in the volume and quality of available data. These advances combine to make chronic-disease data-bank systems an increasingly valuable part of the armamentarium of clinical research.

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Clinical Decision Analysis Using Microcomputers

A Case of Coexistent Hepatocellular Carcinoma and Abdominal Aortic Aneurysm

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Many difficult medical decisions involve uncertainty. Decision analysis—an explicit, normative and analytic approach to making decisions under uncertainty—provides a probabilistic framework for exploring difficult problems in nondeterministic domains. As the methodology has advanced, clinical decision analysis has been applied to increasingly complex medical problems and disseminated widely in the medical literature. Unfortunately, this approach imposes a heavy computational burden on analysts. Microcomputer-based decision-support software can ease this burden.

(Wong JB, Moskowitz AJ, Pauker SG: Clinical decision analysis using microcomputers—A case of coexistent hepatocellular carcinoma and abdominal aortic aneurysm, *In* Medical informatics [Special Issue]. West J Med 1986 Dec; 145:805-815)

Uncertainty—in diagnosis, in prognosis and in quality of life—is common in medical decision making. Over the past decade, an explicit, normative and analytic approach to making decisions has gained an increasing following in medicine: decision analysis has been applied to choices facing individual patients and policy analysts alike. Its theoretic foundations lie in probability theory, game theory and utility theory. Its first application was in the 1960s in industry and in the early 1970s in medicine, and currently medical applications are one of the most active areas of decision analysis research.[1-3]

Decision analysis "techniques" include Bayesian analysis, state transition models and "decision tree" models, to name just a few. They each address slightly different questions. In this article we focus on structuring a clinical problem as a "decision tree" and examine the selection of therapy for a patient with a large abdominal aortic aneurysm and hepatocellular carcinoma. We use this real clinical case to explore the benefits and limitations of some current decision analysis computer software that can be used to construct and analyze decision models.

Basics of Decision Analysis

Clinical decision analysis involves seven fundamental steps. First, the question must be framed compactly as a choice among a limited set of alternatives. Second, the problem is structured explicitly, separating choices (decisions) from chance events and providing a clear description of each possible outcome. We shall use a decision tree to express this structure. Third, all possible chance events are assigned relative likelihoods on a probability scale. Fourth, all possible outcomes are assigned utilities on a single consistent scale. Fifth, the average or expected utility of each strategy is calculated, using a weighted average for each chance event and a maximization operation—that is, picking the best—at each decision point. Sixth, and most important, the sensitivity of the model is analyzed to determine the effects of variations of its assumptions. Seventh, the results of the analysis are interpreted to provide a clinician unfamiliar with these techniques insights about the clinical problem.

Case Example

Case Presentation

The patient, a 73-year-old man with diabetes mellitus and hypertension, sought medical attention for headaches. He was discovered to have a mass in his liver and an elevated hematocrit. On further evaluation the hepatic mass was found to be solitary and predominantly in the right lobe, with extension into the caudate lobe; it measured 8 by 11 by 10 cm. He was coincidentally found to have a 5.8-cm abdominal aortic aneurysm. On percutaneous liver biopsy, the specimen showed cell clusters with malignant morphologies suggestive of hepatocellular carcinoma. Viral studies for hepatitis B showed antibodies to core antigen, but neither surface antigen

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ABBREVIATIONS USED IN TEXT

AAA = abdominal aortic aneurysm
ASR = age, sex and race
ASVD = atherosclerotic vascular disease
DEALE = declining exponential approximation of life expectancy
STM = short-term morbidity

nor surface antibody. The serum α-fetoprotein level was 74,500 μg per liter (normal < 20), corroborating the diagnosis of hepatocellular carcinoma.

The Question Stated

Given the presence of hepatocellular carcinoma, which severely limits the patient's life expectancy, and the presence of an abdominal aortic aneurysm (AAA), which has the potential for catastrophie rupture but may not do so in this patient's limited lifetime, which of the following management options would be optimal?

- No further evaluation or treatment for either the hepatoma or aortic aneurysm
- Give chemotherapy alone (5-fluorouracil) for the hepatoma without further workup to determine its resectability and without attempting to repair the aneurysm
- Repair the aneurysm in addition to giving chemotherapy for the hepatoma
- Do further workup of the hepatoma to determine its resectability but do not repair the aneurysm
- Do a workup for and resect the hepatoma, if localized, and repair the aneurysm regardless of the resectability of the hepatoma
- Do further workup for the hepatoma with resection, if localized, and repair the aneurysm only if the hepatoma is resectable.

Randomized, controlled, prospective trials of patients with hepatocellular carcinoma and coexistent abdominal aortic aneurysm do not exist. The literature does, however, provide data about the survival of patients with hepatocellular carcinoma and separate data about the survival of patients with abdominal aortic aneurysm. Using decision analysis, we incorporated these two separate sources of information, along with information about the quality of life associated with the alternative interventions, into a model that provides a recommendation for this patient and insight about this clinical dilemma.

Structuring the Decision

Assumptions in the model. Because of limitations in the data available and to simplify the model so it facilitates, rather than obscures, insight into the problem, we made the following assumptions:

- We assumed that a surgeon's judgment about the feasibility of resecting the hepatoma is both 100% sensitive and 100% specific. Because there is no gold standard for the resectability of such tumors, this definition has the effect of assuming a good match between the surgeon's judgment about the feasibility of resection (in terms of tumor location rather than tumor size) and our separate assumptions about prognosis based on that classification.
- We assumed that the prognosis of a case of hepatoma either without treatment or with chemotherapy is not affected by whether or not resecting the tumor is technically feasible.
- We did not adjust estimates of quality of life for the effects of chemotherapy. Hepatocellular carcinoma is treated mostly by administering 5-fluorouracil, a relatively nontoxic drug.
- In estimating this patient's life expectaney, we did not consider the excess mortality rate associated with his diabetes mellitus as he had no clinical evidence of microvascular disease and required only diet for control.
- We assumed that after successful repair of the aneurysm, the subsequent risk of rupture is zero. The modern surgical technique of covering the prosthesis with the adventitia of the aneurysm acts to separate the prosthesis from the intestine and virtually eliminates the chance of rupture or erosion into the duodenum.

Building the tree. The next step in clinical decision analysis is to structure the problem explicitly, distinguishing choices from chance events under the control of neither physician nor patient. In this model we use a "decision tree." Decision trees represent the unfolding clinical course of a patient, where the temporal sequence of events is displayed to provide a detailed view of the problem.

Conventionally there are three types of events or nodes in a decision tree: decision nodes (denoted as squares), chance nodes (denoted as circles) and terminal nodes (denoted as rectangles). We also use an arrow to indicate the automatic institution of a therapy after a particular chance event or test result. The decision tree in Figure 1 uses these conventions.

Starting at the square decision node, labeled CHOOSE at the far left on the figure, we see six branches representing alternative strategies. The top branch, labeled NO THERAPY, represents treating neither the patient's hepatoma nor repairing his aneurysm. This branch ends in a rectangular terminal node that will contain its utility.

The second branch of the decision node, labeled CHEMOTHERAPY ONLY, represents the strategy of using empiric chemotherapy for the hepatoma but not repairing the aneurysm. Again, the rectangular terminal node will contain the utility associated with this outcome.

The third branch of the decision tree, labeled AAA REPAIR ONLY, denotes the strategy of repairing the aneurysm without doing a workup for the hepatoma. This branch leads to a circular node representing the chance that the patient may die during the operation (DIE AAA REPAIR). If he survives, his hepatoma will remain unresected. The arrow here indicates that these patients will be given empiric chemotherapy.

The fourth branch of the decision node, HEPATIC WORKUP, represents the strategy of working up the patient for the hepatoma but not repairing the aneurysm. This branch leads to the circular node representing the chance that the hepatoma appears to be resectable. If the tumor is resectable, the patient may survive the surgieal procedure. If his tumor is not resectable, he is nonetheless given chemotherapy. In either case, his prognosis is still limited by the aneurysm.

The fifth branch of the decision node denotes the strategy of working up for the resectability of the hepatoma and repairing the aneurysm (BOTH HEPATIC WORKUP & AAA REPAIR). It is identical to the HEPATIC WORKUP strategy except that if the patient survives hepatic resection or if the tumor is not amenable to resection, he will undergo aneurysm repair. If he survives that operation and his tumor is resected, then he receives no further therapy. If, on the other hand, his

hepatoma is not resectable and he survives the aneurysm repair, chemotherapy is administered.

The last branch of the decision node, SELECTIVE AAA REPAIR, represents the strategy of doing a workup for the hepatoma but repairing the aneurysm only if the tumor was resected. It duplicates the BOTH strategy except that if the tumor is not resectable, the aneurysm will not be repaired and the patient will receive chemotherapy.

Assignment of Probabilities

Hepatocellular carcinoma. Five aspects of hepatocellular carcinoma were modeled in the decision: (1) the probability that the lesion will be resectable, (2) the mortality rate associated with resection, (3) the natural history of hepatoma, (4) the prognosis of patients treated with chemotherapy and (5) the prognosis after successful resection. Tables 1 and 2 list the base-line values that we used for these variables.

The probability that the lesion is resectable (0.13) was derived from the combined data of ten clinical studies, involving nearly 4,500 patients.[4-13] The operative mortality for resecting a hepatoma (0.19) was based on 17 studies involving more than 1,000 patients.[4-6,8-11,13-22] To determine excess mortality rates, we adjusted each study's data for the mortality rate of the general population[23] matched to the study population for age, sex and race so that the calculated excess rate reflects only the contribution of disease to mortality.[24,25] The resulting excess mortality rates can then be treated as independent contributors to the overall mortality rate and life expectancy, allowing their use with patients of age, sex or race different from those of the original study group.[24,25] The survival of patients with untreated hepatocellular carcinoma ranges from two to four months,[26-28] for an excess monthly mortality rate of 0.25. With chemotherapy, median survival

TABLE 1.—*Base-Line Probabilities for Decision Tree*

Factors	*Value*
Probability	
Of resectable hepatoma	0.13
Of dying at hepatoma resection	0.19
Of dying at elective abdominal aortic aneurysm repair	0.07
Efficacy*	
Of chemotherapy in hepatocellular carcinoma	0.65
Of surgical treatment in hepatocellular carcinoma	0.88

*The efficacy of each intervention is the ratio of the mortality rate of treated to untreated disease.

TABLE 2.—*Base-Line Rates and Quality-Adjustments for Declining Exponential Approximations of Life Expectancy*

Factors	*Symbol*	*Value*
Mortality Rates, Monthly		
Base-line age, 73-year-old man	μ_{ASR}	0.0085
Excess		
Hepatocellular carcinoma	$\mu_{HEPATOMA}$	
Untreated		0.250
Treated with chemotherapy		0.088
Treated with surgery		0.031
Abdominal aortic aneurysm (AAA), 5.8 cm	μ_{AAA}	0.0048
Atherosclerotic disease*	μ_{ASVO}	0.0028
Short-Term Morbidity (STM), Months		
Abdominal aortic aneurysm repair	$STM_{(AAA\ REPAIR)}$	0.50
Hepatoma resection	$STM_{(HEPATIC\ RESECTION)}$	0.75
Hepatic workup	$STM_{(HEPATIC\ WORKUP)}$	0.25

ASR = age, sex, race; ASVO = atherosclerotic vascular disease

*Based on the excess mortality rate of an age-, sex- and race-related cohort with abdominal aortic aneurysms who survive aneurysm repair.

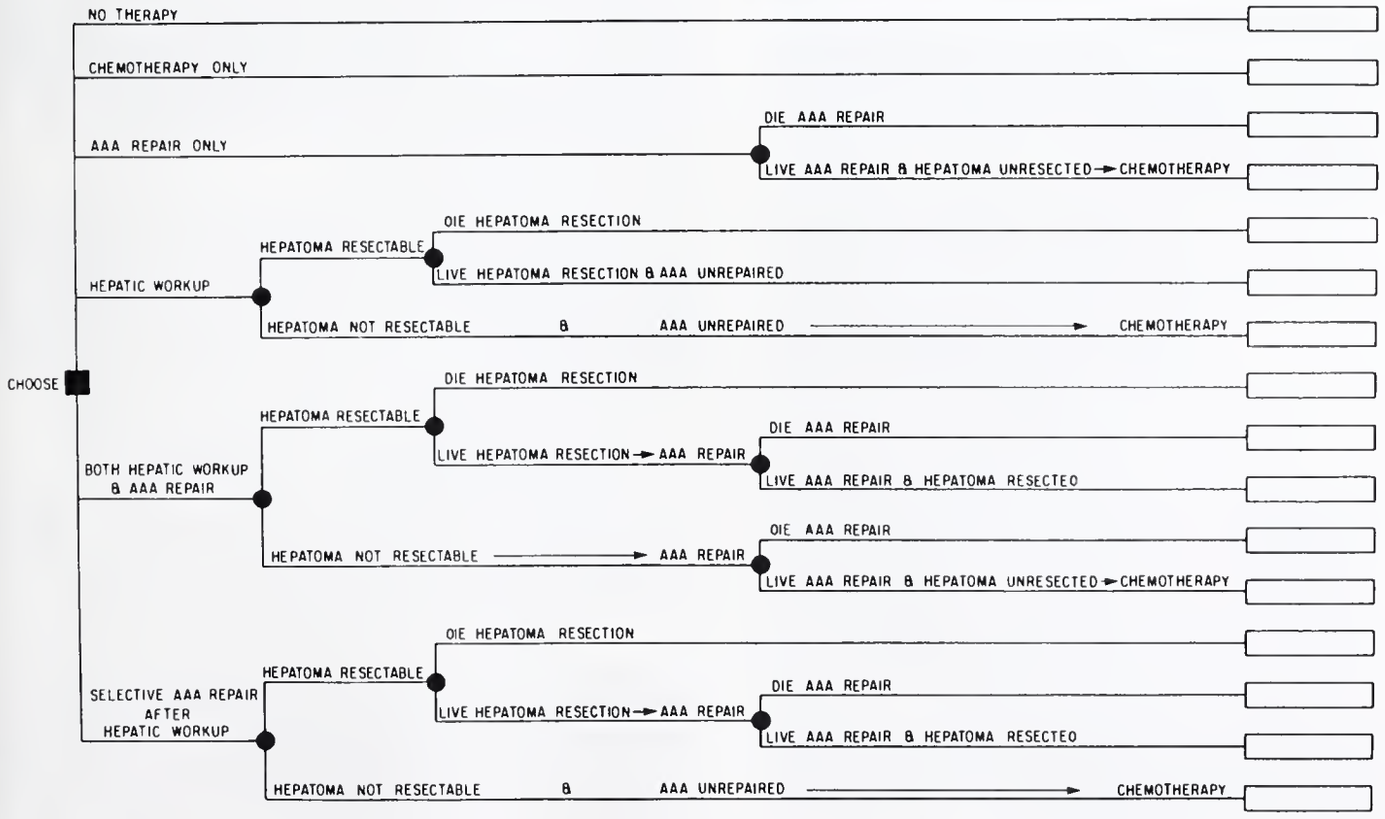

Figure 1.—A decision tree: The decision node is designated by a square, chance nodes by circles and terminal nodes are represented by rectangles. Each of the six branches leading from the decision node represents a different strategic option.

is 5 to 11 months[24,29,30] for an excess monthly mortality rate of 0.088 and an efficacy of 0.65. Combining the results of 15 studies involving 657 patients who survived hepatic resection, the calculated five-year survival is 15.3%,* yielding an excess monthly mortality rate of 0.031 and an efficacy of 0.88.

Abdominal aortic aneurysm. Based on five studies of patients older than 70 years, elective aneurysm repair carries a 0.07 operative mortality, while emergency repair is associated with a 0.73 mortality rate.[32-36] This rate is for patients who reach the operating room, but 35% of patients with ruptured aneurysms die before a surgical repair can be done.[37,38] Thus, 0.18, or 0.65 $\times$ 0.27, of patients older than 70 years will survive rupture of the abdominal aortic aneurysm for an overall mortality rate of 0.82. The most important predictor of the risk of rupture is size.[39] Based on Rutherford's data,[39] the probability of a 5.8-cm aneurysm rupturing is 0.069 per year or 0.0059 per month. Multiplying, then, the monthly probability of rupture (0.0059) by the probability of mortality if rupture occurs (0.82) yields a monthly excess mortality rate of 0.0048 for the aneurysm (Table 2).

In addition to their risk of aneurysm rupture, patients with abdominal aortic aneurysms are at risk of dying of associated coronary artery and cerebrovascular disease. To determine the excess mortality rate attributable to these atherosclerosis-related causes, we compiled data from 20 studies of more than 5,000 patients who have survived abdominal aortic aneurysm repair.[32,33,40-57] These patients died at a monthly rate that was 0.0028 higher than expected for patients of the same age, sex and race from the general population (Table 2).[23]

Assignment of Utilities

We used quality-adjusted life expectancy, measured in quality-adjusted life months, to specify the relative value of outcomes beyond the short-term horizon of the decision tree. Such quality-adjusted life expectancies reflect both length and quality of life. Life expectancy was calculated using the declining exponential approximation ("DEALE")[24,25] and then was adjusted for the short-term morbidities that might be experienced by the patient.

The "DEALE" is a convenient technique for approximating life expectancy when a patient does not "match" the literature closely because that patient has several diseases or is a different age from that of patients in a reported series. The method is based on a simple declining exponential curve of the form, $e^{-\mu T}$. Life expectancy, defined as the area under a survival curve, is equal to the reciprocal of the average mortality rate ($1/\mu$) for such a simple exponential. Empirically, the reciprocal of the *average* mortality rate approximates the area beneath actual survival curves of cohorts of similar patients. Although some components of yearly mortality rates increase exponentially with age, according to Gompertz's law,[58] the DEALE uses an average yearly mortality rate to calculate survival. This average rate is composed of two parts:

1. The base-line average mortality rate μ_{ASR}, determined by the demographics of age, sex and race (ASR) (calculated as the reciprocal of the life expectancy found in tables of vital statistics of the general population); and

2. Excess mortality rates imposed by various diseases (obtained from sources in the literature). An excess mortality rate is associated with *each* disease process.

The life expectancy of a person who has several diseases is found by adding the base-line mortality rate (μ_{ASR}) to the excess mortality rates of each disease and taking the reciprocal of that sum:

$$1/(\mu_{ASR} + \mu_{DISEASE\text{-}1} + \mu_{DISEASE-2} + \ldots + \mu_{DISEASE\text{-}N}).$$

The life expectancy for this patient is then approximately

$$1/(\mu_{ASR} + \mu_{ASVD} + \mu_{AAA} + \mu_{HEPATOMA}).$$

μ_{ASVD} is the excess mortality rate from generalized atherosclerotic vascular disease, such as cerebrovascular and coronary artery diseases. Because of the high prevalence of such diseases in patients with aortic aneurysm, we must consider such factors in the calculation of life expectancy. μ_{AAA} is the excess mortality rate attributable to aneurysm rupture (calculated above), and $\mu_{HEPATOMA}$ is the excess mortality rate imposed by the hepatocellular carcinoma and a given treatment strategy. Table 2 summarizes the base-line values of these aspects for this patient.

After calculating life expectancy using the DEALE, we adjust for the short-term morbidity (STM) associated with each treatment by subtracting a fraction of the time spent at less than full quality of life. The complete formulation of quality-adjusted life expectancy for this patient is then

$$1/(\mu_{ASR} + \mu_{ASVD} + \mu_{AAA} + \mu_{HEPATOMA}) - STM_{(HEPATOMA\ WORKUP)} - STM_{(HEPATOMA\ RESECTION)} - STM_{(AAA\ REPAIR)}$$

Recall that we have chosen to ignore the short-term morbidity of chemotherapy and the long-term morbidities of hepatoma resection and aneurysm repair. The quality-adjusted life expectancies for each of the terminal nodes of the tree are calculated from this equation, except for perioperative death, which is assigned a utility of zero. If a possible short-term morbidity does not occur in a particular strategy, such as $STM_{(HEPATOMA\ RESECTION)}$ in the AAA REPAIR ONLY strategy, its value is zero. The values for the individual mortality rates and quality adjustments are summarized in Table 2.

Base Case Expected Utility

Figure 2 provides the probabilities and utilities omitted from Figure 1. Each of the six strategies is composed of a "path." For example, looking at the strategy labeled HEPATIC WORKUP, we can trace one path by following the upper branch at the first chance node and the lower branch at the second chance node:

HEPATIC WORKUP→HEPATOMA RESECTABLE→LIVE HEPATOMA RESECTION & AAA UNREPAIRED

The probability of achieving a given outcome is just the product of all of the probabilities along the path (the numbers underneath each branch name in Figure 2), such as

$$0.13 \times 0.81 = 0.1053, \text{ approximately } 0.105$$

for the path above. Table 3 summarizes the utility attached to the outcome of a path and the probability of each path, except for paths where the patient dies because the utility of these branches is zero. The *average or expected utility of a path* is the product of the path probabilities times the path outcome utility.

The *expected utility of a strategy* is just the sum of the

*References 4-6, 8-13, 15, 17, 19-21, 31.

expected utilities of its paths. The base-line expected utility for each strategy (Table 3), in quality-adjusted months, is as follows:

NO THERAPY	3.76 months
CHEMOTHERAPY ONLY	9.61 months
AAA REPAIR ONLY	8.90 months
HEPATIC WORKUP	10.27 months
BOTH HEPATIC WORKUP & AAA REPAIR	9.71 months
SELECTIVE AAA REPAIR	10.31 months

The best and the worst outcomes differ by about seven months, which is substantial (64% of the best). Thus, the NO THERAPY strategy would be quite suboptimal. The four best strategies, however, differ by only 21 days (7%), a relatively "close call." Of these four, SELECTIVE AAA REPAIR is the best, whereas CHEMOTHERAPY ONLY is the least invasive and least costly.

Because the NO THERAPY strategy was unequivocally inferior to the other five, we have eliminated it from further discussion.

Sensitivity Analysis

As clinicians, we recognize that probabilities obtained from the literature are inexact and may not be precisely relevant to a particular patient. Sensitivity analysis permits analysts to ask "What if?" and investigate the impact of variations in their assumptions. Herein lies a major benefit of decision analysis. An analyst can examine the plausible range of values for each variable and determine if the optimal strategy changes with these revised values. The range is chosen to have a high likelihood of containing the "correct" value for the variable in question.

One-way analyses. In a one-way sensitivity analysis, we change one variable and recalculate the expected value of each strategy. The results can be presented in a graphic format with the variable on the horizontal axis and expected utility of each strategy on the vertical axis. Figure 3 summarizes a one-way sensitivity analysis in which aneurysm size (horizontal axis) changes. Each strategy corresponds to a line showing how its expected utility varies as a function of the independent variable. As aneurysm size increases, strategies that do not include aneurysm repair decline in expected utility because larger aneurysms are more likely to rupture. Notice that the solid line representing SELECTIVE AAA REPAIR and the dotted line representing HEPATIC WORKUP cross where the aneurysm size is 5.5 cm. This value is called a "threshold point." If the aneurysm were smaller than this value, then the risk of aneurysmectomy would outweigh the risk of spontaneous rupture, and HEPATIC WORKUP alone would be the preferred strategy. On the other hand, if the aneurysm were larger than 7.4 cm, the optimal strategy would be the BOTH strategy because of the risk of imminent rupture. Because the base-line value is very close to the threshold point, the decision is quite sensitive to aneurysm size. A close-call decision is generally sensitive to a variety of factors.

What if the operative mortality were different? The one-way sensitivity analysis in Figure 4 displays the probabilities of dying at hepatoma resection and at aneurysm repair on the horizontal axis. Quality-adjusted life expectancy is again displayed on the vertical axis. Because operative mortality is related to a patient's general and cardiovascular condition, factors influencing the risk of one surgical procedure affect the risk with another—they are not independent. Therefore, we "link" the risk of aneurysm repair to that of hepatoma resection so that increasing one increases the other. In Figure 4, as the probability of perioperative death rises, the expected

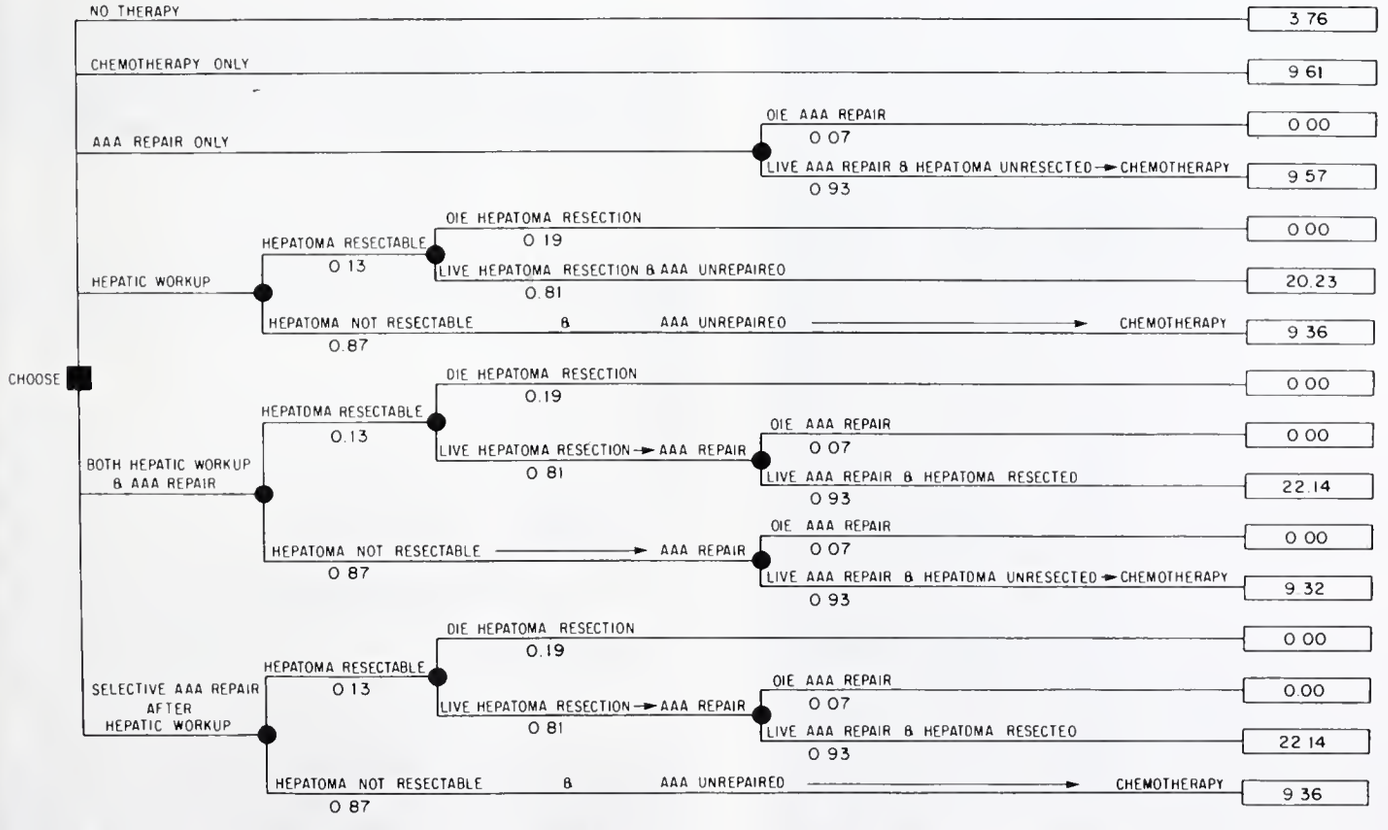

Figure 2.—The decision tree is shown with base-line probability and utility values. The probabilities are located beneath each chance node branch and utilities are within the rectangular terminal nodes. Utilities are calculated in Table 3.

TABLE 3.—*Using DEALE to Calculate the Quality-Adjusted Life Expectancy (QALE) of Outcomes and Strategies*

Path Outcome	μ_{ASR}	μ_{ASVD}	μ_{AAA}	$\mu_{HEPATOMA}$	μ	$1/\Sigma\mu$	$STM_{(HEPATIC\ WORKUP)}$	$STM_{(HEPATOMA\ RESECTION)}$	$STM_{(AAA\ REPAIR)}$	QALE	Probability	P X QALE Utility
No Therapy	0.0085	0.0028	0.0048	0.250	0.2661	3.76	0	0	0	3.76	1.0	3.76
										Expected Utility =		3.76
Chemotherapy Only	0.0085	0.0028	0.0048	0.088	0.1041	9.61	0	0	0	9.61	1.0	9.61
										Expected Utility =		9.61
AAA Repair Only												
Live AAA Repair & No Hepatoma Workup	0.0085	0.0028	0.0000	0.088	0.0993	10.07	0	0	0.50	9.57	0.93	8.90
										Expected Utility =		8.90
Hepatic Workup												
Live Hepatoma Resection & AAA Unrepaired	0.0085	0.0028	0.0048	0.031	0.0471	21.23	0.25	0.75	0	20.23	0.1053	2.13
Hepatoma Not Resectable & AAA Unrepaired	0.0085	0.0028	0.0048	0.088	0.1041	9.61	0.25	0	0	9.36	0.8700	8.14
										Expected Utility =		10.27
Both Hepatic Workup & AAA Repair												
Live Hepatoma Resection & Live AAA Repair	0.0085	0.0028	0.0000	0.031	0.0423	23.64	0.25	0.75	0.50	22.14	0.0979	2.17
Hepatoma Not Resectable & Live AAA Repair	0.0085	0.0028	0.0000	0.088	0.0993	10.07	0.25	0	0.50	9.32	0.8091	7.54
										Expected Utility =		9.71
Selective AAA Repair After Hepatic Workup												
Live Hepatoma Resection & Live AAA Repair	0.0085	0.0028	0.0000	0.031	0.0423	23.64	0.25	0.75	0.50	22.14	0.0979	2.17
Hepatoma Not Resectable & AAA Unrepaired	0.0085	0.0028	0.0048	0.088	0.1041	9.61	0.25	0	0	9.36	0.8700	8.14
										Expected Utility =		10.31

AAA = abdominal aortic aneurysm; ASR = age, sex, race; ASVD = atherosclerotic vascular disease; DEALE = declining exponential approximation of life expectancy; STM = short-term morbidity

utility of strategies involving surgical repair declines. The only strategy not involving an operation, CHEMOTHERAPY ONLY, is unaffected. When the probability of dying at hepatoma resection falls between 0.24 and 0.45 and the probability of dying at aneurysm repair falls between 0.09 and 0.17, HEPATIC WORKUP is optimal; for probabilities below this range, SELECTIVE AAA REPAIR is best. For probabilities above this range, CHEMOTHERAPY ONLY is the best option. The decision, then, is quite sensitive to the likelihood of surgical mortality.

What if the efficacy of hepatic resection in this patient were lower than originally estimated? For example, what if review of the histologic sections showed invasive cells not originally appreciated? The one-way sensitivity analysis in Figure 5 displays the efficacy of surgical resection in reducing the excess mortality rate of hepatocellular carcinoma along the horizontal axis and quality-adjusted life expectancy along the vertical axis. For efficacies below 0.80, CHEMOTHERAPY would be optimal. If the efficacy were between 0.80 and 0.85, HEPATIC WORKUP would be preferred. For efficacies above 0.85, SELECTIVE AAA REPAIR is best.

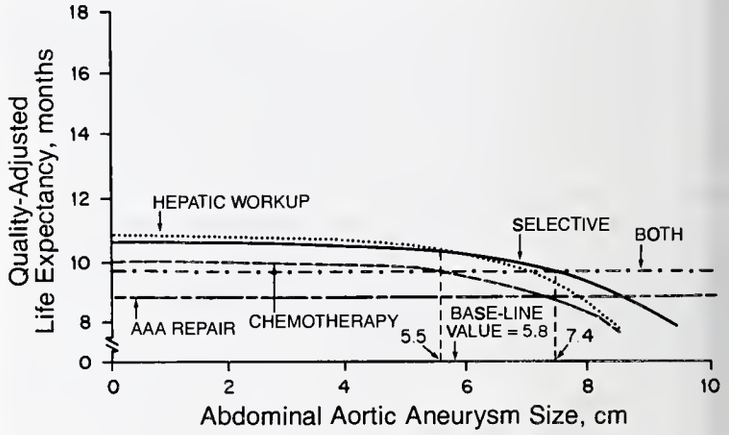

Figure 3.—The graph shows one-way sensitivity analysis of quality-adjusted life months (vertical axis) versus abdominal aortic aneurysm size in centimeters (horizontal axis). The base-line aneurysm size, 5.8 cm, and the threshold values of 5.5 and 7.4 cm are indicated by arrows.

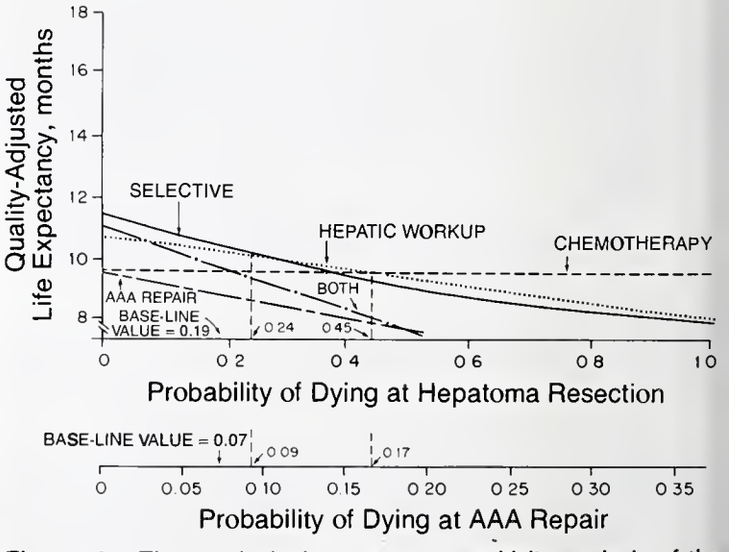

Figure 4.—The graph depicts one-way sensitivity analysis of the probabilities of operative death during hepatoma resection and elective abdominal aortic aneurysm (AAA) repair. The base-line values are 0.19 and 0.07, and the threshold values of 0.24, 0.45, 0.09 and 0.17 are indicated by arrows.

Figure 6 examines the probability of the hepatoma being resectable. CHEMOTHERAPY becomes favored only when this value falls below 0.03. Because this threshold is less than a fourth of the base-line value, the decision is relatively insensitive to what might intuitively be viewed as an important variable. Thus, a decision that is a close call is not necessarily sensitive to *all* aspects.

Two-way analyses. A two-way sensitivity analysis examines the effect of varying two variables simultaneously. It can be interpreted in three ways. From the first perspective, a two-way analysis specifies which strategy is optimal for all combinations of the two variables in question. For example, Figure 7 examines the relationship between the probabilities of dying during hepatoma resection and aneurysm repair (horizontal axis) and the probability that the hepatoma is resectable (vertical axis). Each point on the graph corresponds to a unique combination of the two variables. At each point, one of the six strategies is optimal. We can, therefore, define regions where a specific strategy should be chosen. Three strategies, SELECTIVE AAA REPAIR, HEPATIC WORKUP and CHEMOTHERAPY, dominate the others. Our base-line assumptions (denoted by an X) fall well within the area where SELECTIVE AAA REPAIR is preferred. If we accept the base-line probability that the hepatoma is resectable (0.13) and move horizontally toward the shaded region, we see that the operative mortality would have to increase from the base line of 0.19 to just 0.24 before HEPATIC WORKUP would be preferred. If we continue to move horizontally, then CHEMOTHERAPY would be optimal beyond a probability of 0.45. Similarly, if we accept the base-line value for the mortality of hepatoma repair (0.19) and move vertically, the probability that the tumor is resectable would have to fall considerably (to 0.03) before CHEMOTHERAPY would be preferred. Thus, a two-way sensitivity analysis contains the zones of actions provided in the separate one-way sensitivity analyses (Figures 4 and 6) but omits the strength of preference or expected utility of each option.

From a second perspective, a two-way sensitivity analysis describes how the threshold value of one variable changes as a second variable also changes. Again, referring to Figure 7, the curves specify how the threshold probability of resectability (vertical axis) shifts as the operative mortalities of hepatoma resection and of aneurysm repair (horizontal axis) change. The lower the probability of dying at hepatoma resection and aneurysm repair, the lower the threshold for choosing HEPATIC WORKUP or SELECTIVE AAA REPAIR.

A third perspective is that a two-way sensitivity analysis shows how a zone of strategic action is affected by changing another assumption. In Figure 4, we observed a zone of mortality rates for which HEPATIC WORKUP is the strategy of choice. In Figure 7, we see that the hatched zone widens as

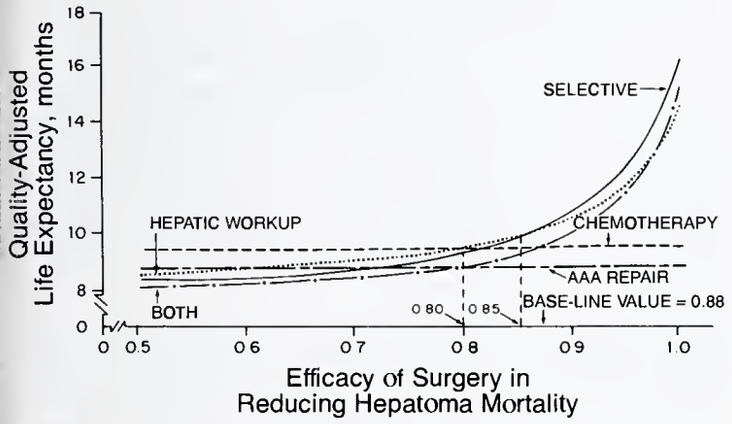

Figure 5.—The graph shows one-way sensitivity analysis of the efficacy of surgery in reducing mortality from hepatoma. AAA = abdominal aortic aneurysm

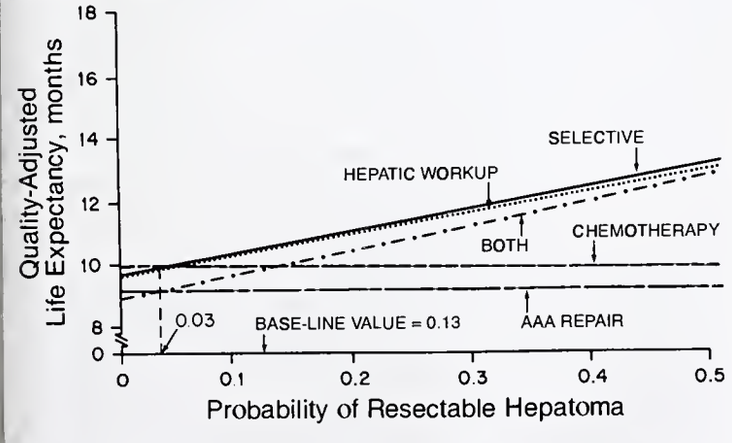

Figure 6.—The graph depicts one-way sensitivity analysis of the probability of the hepatoma being resectable. AAA = abdominal aortic aneurysm

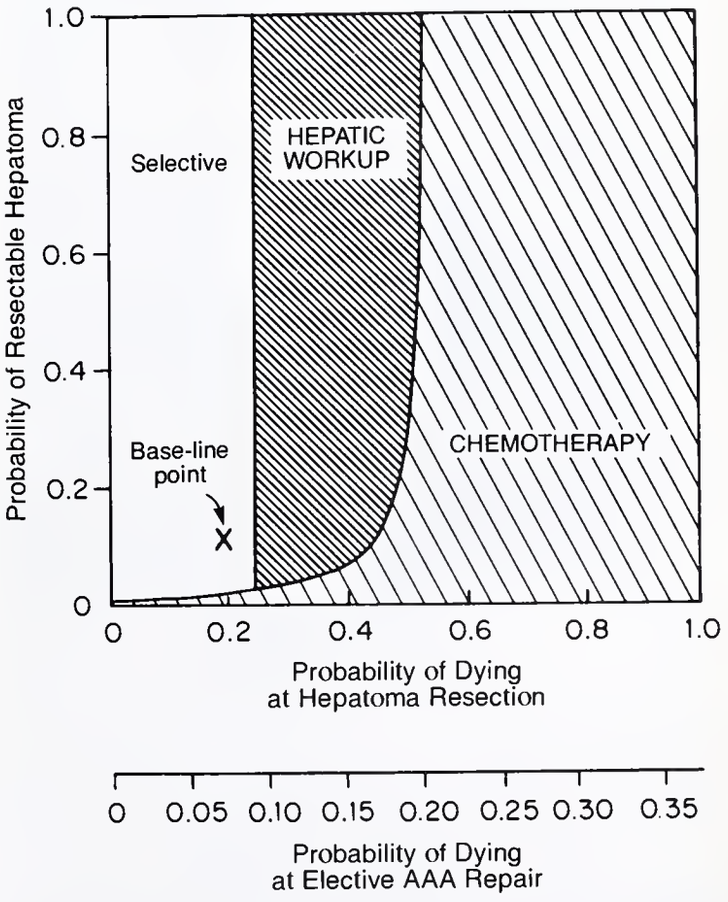

Figure 7.—The graph shows two-way sensitivity analysis of the probability that the hepatoma is resectable (vertical axis) and the mortalities of hepatoma resection and abdominal aortic aneurysm (AAA) repair (horizontal axis). CHEMOTHERAPY ONLY is favored for all points falling in the shaded region to the right of the curved line, HEPATIC WORKUP is optimal for all points falling in the middle region shaded with narrow stripes and SELECTIVE AAA REPAIR is preferred for all points falling in the unshaded region to the left of the curve. The base-line point is indicated by an "X."

the probability that the hepatoma is resectable increases. If the probability of resectability is below 0.04, that zone of action disappears entirely, and if the probability is below 0.02, the zone of action for SELECTIVE AAA REPAIR also disappears.

What if the patient's aneurysm were larger and operative mortality was increased? Figure 8 displays the probabilities of dying at hepatoma resection and at elective abdominal aortic aneurysm repair along the horizontal axis and aneurysm size along the vertical axis. When the probability of dying at elective aneurysm repair is high or the aneurysm is small to moderate in size—that is, the lower right region in the graph—CHEMOTHERAPY would be preferable because the aneurysm would limit life expectancy enough to obviate hepatic workup. If the operative mortality is lower and the aneurysm is small, then HEPATIC WORKUP would be optimal because the risk of rupture is small. For slightly larger aneurysms (4 to 6 cm) where the operative mortality remains the same, resection should only be undertaken after successful hepatoma resection (SELECTIVE AAA REPAIR). For aneurysms greater than 6 cm and low mortality rates, BOTH would be preferable because the risk of spontaneous rupture would then outweigh the operative risk for aneurysm repair. For large aneurysms in the upper right region (Figure 8),

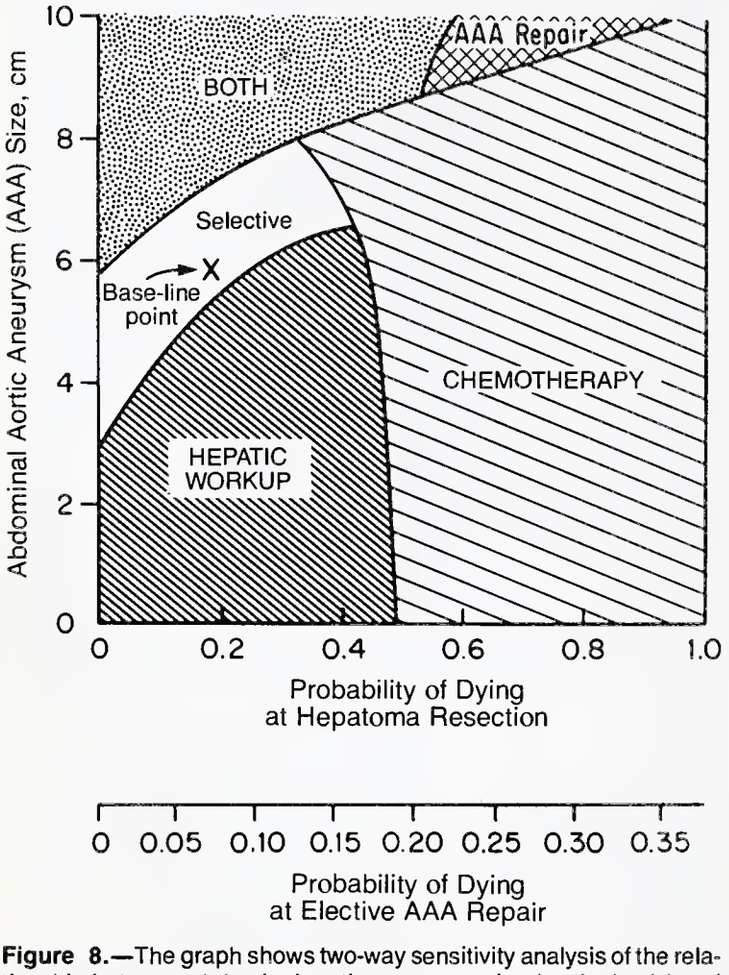

Figure 8.—The graph shows two-way sensitivity analysis of the relationship between abdominal aortic aneurysm size (vertical axis) and the probability of dying at hepatoma resection and at elective AAA repair (horizontal axis). For the region with narrow stripes, HEPATIC WORKUP is preferred. In the region filled with dots, BOTH AAA REPAIR & HEPATIC WORKUP is preferred. SELECTIVE AAA REPAIR is best in the unshaded region, AAA REPAIR is optimal in the region shaded with crosshatching and CHEMOTHERAPY ONLY is favored in the small region shaded with wide stripes. The base-line point is indicated by an "X."

AAA REPAIR would be preferred because the high operative mortality makes hepatoma resection prohibitive; yet, mortality from aneurysm rupture surpasses that from hepatoma.

Figure 9 examines the interplay between the efficacy of hepatic resection and the probability of dying during the surgical procedure. If the efficacy of hepatic resection is low, CHEMOTHERAPY would be optimal (lower region). In the area demarcated with narrow stripes (upper left), the efficacy of hepatoma resection is high enough so that HEPATIC WORKUP would be worthwhile, but life expectancy would be insufficient to warrant AAA repair. When the efficacy of hepatoma resection exceeds 0.73 and operative mortality is low or moderate, aneurysm repair (unshaded region) should be undertaken only if the hepatoma has been successfully resected (SELECTIVE AAA REPAIR).

Clinical Conclusion

The quality-adjusted life expectancies of the four best strategies (SELECTIVE AAA REPAIR, HEPATIC WORKUP, BOTH HEPATIC WORKUP & AAA REPAIR and CHEMOTHERAPY ONLY) are almost indistinguishable. AAA REPAIR ONLY is substantially inferior, and NO THERAPY is the worst under virtually all circumstances. Because our assumptions introduce a slight bias toward a hepatic operation, the expected utility difference between CHEMOTHERAPY ONLY (the lowest valued of the four strategies) and the other three best strategies is slightly overestimated. Indeed, after excluding NO THERAPY and AAA REPAIR ONLY, the decision becomes a "toss-up" or "close call."[59] Surprisingly, the strategy of doing a workup for and resecting the hepatoma is not significantly better than chemotherapy only, largely because of the high operative mortality and morbidity associated with that procedure and the patient's advanced age. Aneurysm repair is not crueial here as rupture is unlikely to occur within the patient's limited lifetime unless the hepatoma is resectable and the efficacy of such an operation is high enough to lengthen the window of risk for aneurysm rupture.

Microcomputer-Based Decision-Support Software

Software to support clinical decision analysis has evolved slowly over the past decade. Currently there is a handful of programs that support decision tree analysis,[60-68] cost-effectiveness analysis,[63-68] Bayesian analysis,[63-66,68] receiver-operating characteristic analysis,[69-72] recursive tree models,[61,63,64,68] Markov state transition models[63,68] and Monte Carlo simulations.[63,65] Although primarily a cottage industry, deeision-analysis software has recently attracted large industry[61] and supports several popular microcomputers, including the IBM PC, AT (personal computer, advanced technology; IBM Corporation, Danbury, Connecticut) and compatibles[60-66,68,69]; the Apple Macintosh,[60] Apple II and III series (Apple Computers, Inc, Cupertino, California)[64,66,67,73]; the Zenith Z89 and Z90 machines (Zenith Data Systems, St Joseph, Missouri),[64,66] and the DEC Rainbow (Digital Equipment Corporation, Maynard, Massachusetts).[62] The programs themselves differ considerably in their analytic capabilities, the sophistication of their graphic displays and their user-friendliness. Herein we explore the general features of decision tree analyzing programs in the context of the present clinical case.

Structuring the Decision Model

The first step in doing any decision analysis is constructing the decision model. Trees can be constructed de novo from the keyboard (in some programs, assisted by a mouse) or from files containing an "orchard" of previously entered trees. Most programs follow one of two modes of keyboard entry: screen-oriented random-access mode in which a semiconstructed tree is displayed on the screen, allowing the analyst to place the cursor at any point in the tree to add, delete or further edit the nodes and branches; and directed-entry mode in which the screen displays the current editing site and the program prompts the analyst to define the nodes and branches of an entire strategy before moving on to another. The first mode of entry allows the analyst to work on any part of the tree at any time and permits saving partially constructed trees for use later. This facilitates incremental construction of decision trees. Most directed-entry-mode programs, however, do provide editing routines for modifying a tree or have a standard output that can be edited by word processing programs. Furthermore, if a decision tree has been recorded on a piece of paper, directed entry saves keystrokes.

Although the modes of tree entry may differ somewhat, the information needed to define the decision trees is the same. Several programs dynamically construct decision trees during evaluation from the information stored in tree files. These files consist of a series of node records with data fields to define the node type—chance, decision and terminal—the names of its daughter nodes, the event probabilities (for chance nodes) and the outcome utilities (for terminal nodes). The more advanced programs support the use of arbitrarily complex algebraic expressions for defining probabilities and utilities. This feature facilitates using well-known probability functions and meaningful utility scales, such as quality-adjusted life expectancy. In fact, some programs permit the use of two different utility scales in the same decision tree, making cost-effectiveness analysis easier.

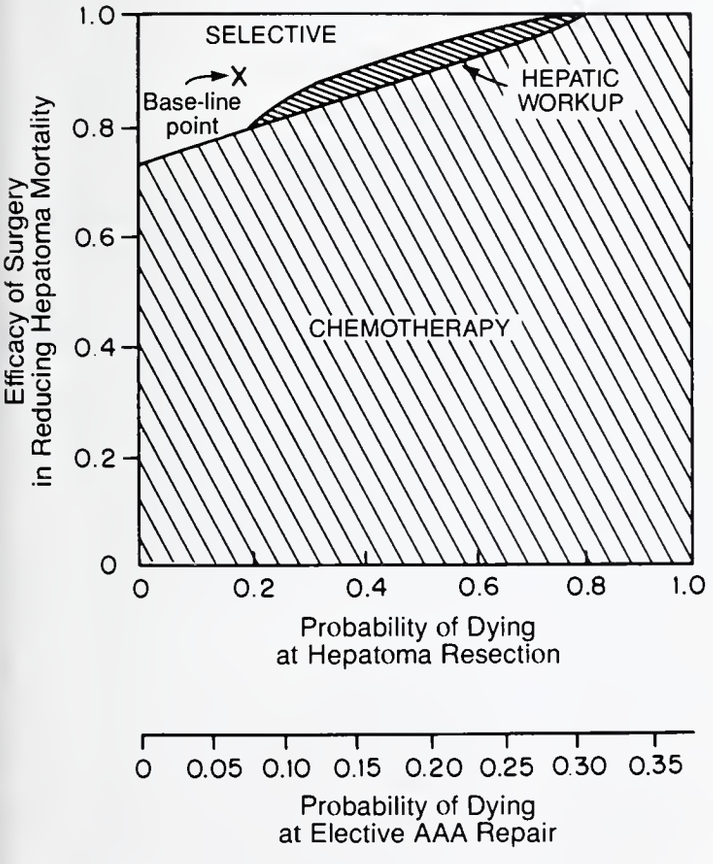

Figure 9.—The graph depicts two-way sensitivity analysis of the efficacy of surgery in reducing hepatoma mortality (vertical axis) and the probability of dying at hepatoma resection and at abdominal aortic aneurysm (AAA) repair (horizontal axis). For all values falling in the region with wide stripes, CHEMOTHERAPY ONLY is preferred. For values falling in the unshaded region (upper left), SELECTIVE AAA REPAIR is preferred. In the region shaded with narrow stripes, HEPATIC WORKUP is preferred. The base-line point is indicated by an "X."

The Evaluation Process

Once a decision tree is entered, it can then be evaluated. To fold back our relatively uncomplicated tree model just once required 152 arithmetic operations (112 additions and subtractions and 40 multiplications and divisions). With a handheld calculator, this process would take between 10 and 15 minutes; with a general tree-folding program, it took microseconds! While one such calculation may not justify the 20 minutes required to enter the tree used for this analysis, the multiple repetitions required for sensitivity analysis clearly do. The one-way sensitivity analysis in Figure 3 required 760 arithmetic calculations. Doing this for all 12 probability variables in the tree involved more than 9,000 calculations. With an average of 3,800 arithmetic operations each, the two-way sensitivity analyses were even more computationally intensive. Yet, each took less than three minutes with a microcomputer.

Graphic Output

Some of the available programs construct sensitivity analysis graphs that resemble the ones shown here, complete with labels. For the most part, the graphs are not of publication quality. Nonetheless, some of the programs mentioned can save the numeric output from an analysis in a form that can be imported into standard spread sheet or graphics programs capable of more professional quality printing.

A Word About Spread Sheets

Although not as efficient, it is possible to use a standard spread sheet program to analyze certain simple decision tree models (E. Jones, "Risk Analysis With 1-2-3," *Lotus* 1985; 1:65-67). A decision tree can be viewed as a spatial organization of probabilities and utilities that can be superimposed on the grid of a spread sheet. One can even use spread sheet "macros" to help establish the expected utility calculations and use spread sheet "tables" to do simple one-way sensitivity analyses. Unfortunately, threshold calculations and two-way sensitivity analyses are very cumbersome. Although this use of such standard programs is possible, the restricted representations available in such programs tend to impede model development in all but the most simplistic cases.

On the other hand, the table used in the expected utility calculation here (Table 3) can be easily implemented as a spread sheet, thereby facilitating at least the simple calculations.

Criticisms

Specialized decision-support software is enormously helpful, if not essential, for doing decision analyses of any complexity; without it, most clinically relevant questions

would be too demanding to tackle. The current generation of software, however, is less than ideal. For first-time users, the start-up cost of learning the conventions of a particular program and the basic concepts of decision analysis is substantial. These programs are not designed to be primary sources for learning decision analysis; they are tools for experienced analysts.

These programs cannot automatically structure a clinical decision, nor can they detect even obvious errors in tree logic or basic methodology. Moreover, the programs are general tools for analyzing decisions, not specifically addressed to the clinical domain. They cannot detect errors in the way data are used, nor can they interpret results to provide clinical insights about a problem. "Debugging" decision trees remains the task of a skillful analyst and clinician. As a rule, we treat decision trees in the same way that we treat computer programs: just as every computer program has a "bug," so does every decision tree. Decision models are always imperfect reflections of the real world and their use must be limited to settings in which their match to reality is "good enough." Structuring a clinical problem as a decision tree is an iterative process of designing and testing. The goal is to reduce the remaining errors sufficiently so that the model is useful for a specific clinical application. We do a broad range of sensitivity analyses to identify the limits of a model's usefulness and to define circumstances in which errors occur.

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The INTERNIST-1/QUICK MEDICAL REFERENCE Project—Status Report

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INTERNIST-1 and its successor, QUICK MEDICAL REFERENCE (QMR), are computer programs designed to provide health care professionals with diagnostic assistance in general internal medicine. Both programs rely on the INTERNIST-1 computerized knowledge base, which comprehensively describes 570 diseases in internal medicine. The philosophies behind the development of each program differ. Whereas INTERNIST-1 functions solely as a high-powered diagnostic consultant program, the QMR program acts more as an information tool, providing users with multiple ways of reviewing and manipulating the diagnostic information in the program's knowledge base. At the lowest level, the program can be viewed as an electronic textbook of medicine. In addition, the QMR program has the ability to assist users with generating hypotheses in complex patient cases. The QMR program has not been evaluated formally as an information tool for practicing physicians. A preliminary study indicates that QMR's case-analysis capabilities are of potential benefit in most patients in internal medicine admitted for diagnostic evaluation.

(Miller RA, McNeil MA, Challinor SM, et al: The INTERNIST-1/QUICK MEDICAL REFERENCE project—Status report, *In* Medical informatics [Special Issue]. West J Med 1986 Dec; 145:816-822)

INTERNIST-1 and its successor, QUICK MEDICAL REFERENCE (QMR), are computer programs designed to provide health care professionals with diagnostic assistance in general internal medicine. We review the past accomplishments, current status and future objectives of our research at the University of Pittsburgh related to the INTERNIST-1/QMR project. Project objectives continue to be to extend and improve the comprehensive INTERNIST-1 medical knowledge base for diagnosis in general internal medicine and to further develop and evaluate related diagnostic information-processing programs.

The INTERNIST-1 Project

INTERNIST-1, an experimental computer-based diagnostic consultant system for general internal medicine, was developed and evaluated by Myers, Pople and Miller and co-workers.[1-7] The original goal of the project, as conceived in 1972-1973, was to develop a diagnostic computer program that could functionally mimic the reasoning of an expert clinician. Given patient data in the form of historical facts, current symptoms, findings from a physical examination and laboratory results, the INTERNIST-1 program was designed to formulate differential diagnoses and then resolve them by asking questions. The program could make multiple and complex diagnoses in challenging patient cases.

In 1981 a retrospective evaluation of the INTERNIST-1 program was conducted using clinicopathological conference (CPC) cases published in *The New England Journal of Medicine* (NEJM).[3] The study was done via retrospective case analyses so as not to subject patients to the risk of possible diagnostic errors by the computer program. The NEJM CPC cases were chosen because they contained enough detail to permit computer analysis. The diagnostic performance of the INTERNIST-1 program (for cases where the ultimate anatomic diagnoses were within the program's knowledge base) was found to be qualitatively similar to that of the clinicians caring for patients at an academic teaching hospital. The program's ability to arrive at the "correct" diagnosis, however, was not as good as that of the invited clinical expert case discussants. The study identified several deficiencies in the

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ABBREVIATIONS USED IN TEXT

CPC = clinicopathological conference
CPCS = Clinical Patient Case Simulator
NEJM = *The New England Journal of Medicine*
PC = personal computer
QMR = QUICK MEDICAL REFERENCE

INTERNIST-1 knowledge base and diagnostic algorithms. The conclusions of the evaluation were that the knowledge base should be completed and that the program was not ready for use as a general-purpose diagnostic consultant system.

The QUICK MEDICAL REFERENCE Project

The Transition From INTERNIST-1 to QMR

A decade of experience spent in producing, testing and refining the INTERNIST-1 knowledge base has provided valuable insights into the difficulties associated with building and maintaining medical expert systems. Problems with the INTERNIST-1 approach to medical diagnosis[5] have led us (R.A.M., F.E.M., J.D.M.) to develop, in 1985-1986, a successor program to INTERNIST-1: Quick Medical Reference, or QMR.[6,8-10] QMR is a microcomputer-based source of information and consultation for diagnosis in general internal medicine. It was developed as a logical extension of the INTERNIST-1 project, with the objective to provide useful medical knowledge rapidly and conveniently to health care professionals. QMR takes advantage of many valuable aspects of INTERNIST-1 while attempting to overcome many of INTERNIST-1's deficiencies.

The INTERNIST-1/QMR knowledge base is a model for developing and maintaining an expert system knowledge base. The most significant achievement of the INTERNIST-1 project has been the creation of an extensive, computer-based repository for medical knowledge regarding the diagnosis of diseases in internal medicine. As of June 1986, the INTERNIST-1 knowledge base encompasses 572 diagnoses in internal medicine, and the system recognizes more than 4,000 possible patient findings. The knowledge base also includes more than 4,000 "links" detailing the causal, temporal and probable interrelationships among the 572 disorders. It is estimated that the number of items of information in the current but still incomplete INTERNIST-1 knowledge base is roughly 250,000. The structure and content of the INTERNIST-1 knowledge base have been described previously.[3,7] QMR uses a modified superset of the INTERNIST-1 knowledge base as its source of medical information.

Because of the expansive domain of the INTERNIST-1 knowledge base, it was not possible to implement methods for constructing computerized medical knowledge bases used by other researchers, such as clinical data banking and "debriefing" of medical experts. For example, excellent clinical data-banking systems have been developed for coronary artery disease by Rosati and associates at Duke University (Durham, NC)[11,12] and for various forms of arthritis and connective tissue disorders by the American Rheumatism Association's ARAMIS project.[13,14]* Clinical data-banking techniques were not appropriate for INTERNIST-1 for two reasons. First, carefully defined entry criteria must be developed to determine which patients' data are eligible for inclusion in a clinical data bank. Developing entry criteria encompassing all diagnoses in internal medicine as a group would have resulted in meaningless generalities. Alternatively, defining entry criteria for each of the 750 diagnoses to be included in the INTERNIST-1 knowledge base would presuppose an existing knowledge base equal in depth and breadth to the INTERNIST-1 knowledge base under development.

With expert systems such as MYCIN[15] and CASNET,[16] methods have been developed for "debriefing" medical experts that were also not applicable to INTERNIST-1. The usual model used in medical "expert systems" for acquiring information requires that the system builders (usually computer scientists) sit down with one or more medical experts to encode the domain experts' factual and heuristic knowledge of a subject.[15-18] INTERNIST-1's domain is so large, however, that it extends beyond the personal expertise of any small group of persons.

The INTERNIST-1 project developed its own methods for collecting and recording medical knowledge. A senior clinician (J.D.M.) who has substantial expertise in the field of medical diagnosis supervised construction of the INTERNIST-1 knowledge base. This investigator has devoted ten full person-years of effort to the project. An additional 50 to 100 persons—junior or senior medical students working under project staff guidance, fellows in computer medicine and faculty members in the Department of Medicine at the University of Pittsburgh—have worked as voluntary contributors in knowledge-base construction.

The following steps are taken during INTERNIST-1/QMR knowledge-base construction:

- Each contributor selects a disease or clinical syndrome not yet described in the INTERNIST-1 knowledge base and reviews the medical literature on the diagnosis of the disorder. One to two weeks of full-time effort are required to examine general and subspecialty textbooks, coupled with a meticulous review of about 50 to 100 relevant, primary journal articles. The goal of the literature survey is to create a list of the clinical abnormalities (findings) that have been reliably and verifiably reported to occur in patients with the given illness. The findings include demographic data and predisposing factors as well as patients' symptoms, signs and laboratory abnormalities. Medical experts who are specialists at the University Health Center of Pittsburgh and other academic centers are consulted to help resolve inconsistencies or deficiencies encountered during the literature review process.

The net result of reviewing the literature and consulting with experts is the creation of a "disease profile"—a list containing an average of 85 findings per disease (range, 25 to 250 findings). In addition to the findings in a disease profile, "linked diagnoses" are identified. Linked diagnoses are those conditions that predispose to the development of the disease under consideration, are causally related to the disease, occur more often than chance in association with the disease or temporally precede the development of the disease.

- After a draft of the disease profile has been compiled, members of the INTERNIST-1/QMR project team review the profile in a seminar led by the senior clinician (J.D.M.). Particular attention is paid during the seminar to maintaining consistency in terminology, comparing the new profile with

*See "ARAMIS (The American Rheumatism Association Medical Information System)—A Prototypical National Chronic-Disease Data Bank," by James F. Fries, MD, and Dennis J. McShane, MD, elsewhere in this issue.

similar existing profiles, reconciling disparate quantitative values from the literature and detecting omissions in the new profile. Participants in the seminar identify aspects of the profile requiring further library review or further input from experts in specialty areas.

- Once a final consensus about the new profile has been achieved, the profile is added to the INTERNIST-1/QMR knowledge base using a knowledge-base editing program.
- A second phase of checking the disease profile for accuracy and completeness then begins, using the INTERNIST-1 (and, in the near future, QMR) diagnostic system as an evaluation tool. The new profile is first tested by presenting the system with a "classic case" of a patient with the disease, constructed from a standard textbook description. The system rarely has difficulty producing the correct diagnosis. The profile is subsequently tested using more difficult CPC cases extracted from individual case reports in medical journals or from available conference proceedings at academic health centers.

Difficult cases have been presented to the diagnostic system on a regular, almost daily basis. It is estimated that over the past decade, a total of 2,000 to 3,000 such cases has been analyzed. By examining the system's inaccurate diagnoses or its failure to make a proper diagnosis, project members review and update "old" disease profiles (those already in the knowledge base). The mechanism for updating is to review the literature further and consult with experts.

- Every two to three years, the entire series of "classic" cases is again analyzed to make certain that changes in the knowledge base (made since the original case analyses) have not adversely affected performance on the cases. Previously run CPC cases are also intermittently reviewed or examined.

Rationale Behind Creating QMR

A major problem with INTERNIST-1 was that the program was designed to serve as a high-powered diagnostic consultant system for challenging cases in internal medicine. The philosophy underlying INTERNIST-1 was that the program should be able to perform as if it were an expert consultant. This model of diagnostic consultation has been important in the subsequent development of the comprehensive INTERNIST-1 medical knowledge base and the related INTERNIST-1 diagnostic program. This model, however, addresses only a small portion of the information needs of physicians.[19] The INTERNIST-1 program did not allow its users to have direct, immediate access to the information in the INTERNIST-1 knowledge base.

In contrast, QMR has been developed in an attempt to meet the practical needs of clinical medicine. The philosophy underlying QMR is that the program should be able to augment a health care professional's diagnostic accuracy and efficiency by providing convenient access to information and a variety of useful tools for managing diagnostic information. The QMR program treats the computer user as an active information-seeking participant, not a passive one, as was the case in INTERNIST-1. In this regard, QMR is similar in purpose to the RECONSIDER program developed by Blois and colleagues.[20]

Another problem with INTERNIST-1 was that the program engaged the user in a laborious, time-consuming dialogue lasting 30 to 75 minutes. This form of interaction was necessary to describe and evaluate a complex patient case comprising 50 to 180 positive and negative findings. Busy physicians, however, can rarely afford this amount of time to interact with a computer program. The problem was compounded by the INTERNIST-1 program's lack of a user-friendly interface. Unless the user entered case findings using the rigid INTERNIST-1 terminology, the program could not process the information. QMR has been designed to provide answers in seconds, rather than minutes or hours.

Whereas INTERNIST-1 was implemented on a mainframe computer with restricted dial-up access, QMR runs on widely available microcomputers. Quick Medical Reference has been written in Turbo Pascal (Borland International). It runs on any system compatible with an IBM personal computer (PC) meeting the following requirements: MicroSoft PC-DOS or MS-DOS disk operating system (version 2.1 or higher), 512K or more of random access memory and at least five megabytes of available space on a fixed (hard) disk. The program runs most efficiently on the IBM-PC-AT (IBM Personal Computer, Advanced Technology model) or compatible 80286-based machines.

Key Features of QMR Program Function

The QMR completer. An important goal of QMR's design is to enable novice users to enter patient findings or diagnoses with ease. QMR's user interface attempts to minimize the amount of typing required from a user and attempts to reduce problems due to spelling errors. A "completer" program has been developed to allow users to enter, quickly and efficiently, the names of the various patient findings and diagnoses known to QMR. The QMR completer allows users to pick a few key words from the medical terms they want to enter and then to type the first few characters of each of those words. The "completer" functions independently of word fragment order—the user obtains the same results no matter how the group of word fragments is typed into QMR. For example, a user wanting to enter the finding "abdominal tenderness, right lower quadrant" could type any of the following:

abd ten low
r l q tender [spaces between r, l and q essential]
lower quadrant

After receiving word fragments as input, the QMR completer displays, within a few seconds, a menu (numbered list) of the possible INTERNIST-1/QMR vocabulary terms matching the fragments entered. Only one or two additional keystrokes are required from the user to select the desired vocabulary item by its menu number.

QMR as a low-level information retrieval tool. QMR contains two useful, straightforward information-retrieval options: (1) "Display a disease profile's findings and links" and (2) "Display the differential diagnosis of a single finding." The disease profile summarizes in a few seconds what would take a person one to two weeks to discover by a primary literature review about the diagnosis of the disease. The findings reliably reported to occur in patients with a given disorder and a list of the linked (related) diagnoses for the disorder are included in the display. Thus, one can easily review a profile of any of the 572 diseases currently in the QMR knowledge base.

The QMR option, "Display the differential diagnosis of a

single finding," allows a user to display the list of possible diagnoses associated with any of the more than 4,000 findings in the knowledge base. In the display, the differential diagnosis is sorted by descending positive predictive value—that is, the most prominent causes of the finding are listed first. The differential diagnosis lists are comprehensive because they are derived from the disease profiles. For example, the differential diagnosis of the finding "abdominal pain, right upper quadrant" contains 131 diagnoses; the differential diagnosis of "chest pain, substernal, at rest" includes 34 diagnoses, and the differential diagnosis of "cyanosis of mucous membranes" includes 103 diagnoses.

QMR as an intermediate-level information management tool. A physician seeing a patient can usually quickly determine that the patient's main pathologic condition involves a particular organ system. The patient, however, may show a finding that does not fit conceptually with disease in that organ system. The QMR option, "Find associations of a finding to a group of diagnoses," can be used to connect a seemingly unrelated finding to disease in a specified organ system. For example, the user can pose the question, "How can massive splenomegaly be related to liver and biliary tract disease?" and determine from the program a list of possible mechanisms. Both direct causes—liver diseases that themselves cause massive splenomegaly—and indirect causes—diseases of the liver and biliary tract that are associated with other diseases that cause massive splenomegaly—are displayed.

For the given example, QMR indicates that the following liver and biliary tract disorders are directly associated with massive splenomegaly: hepatosplenic lymphoma, presinusoidal portal hypertension and sinusoidal or postsinusoidal portal hypertension. Of the liver and biliary tract disorders indirectly related to causes of massive splenomegaly, QMR lists, among others, hepatic amyloidosis as a complication of systemic amyloidosis, hepatic histoplasmosis as a complication of disseminated histoplasmosis, secondary fatty liver as a complication of Felty's syndrome and either hepatic vein thrombosis or cholelithiasis as a complication of paroxysmal nocturnal hemoglobinuria.

QMR also contains a "case analysis" option that can be used in two modes. The first mode is for analyzing simple cases characterized by a dozen or fewer findings. Here a user seeks confirmation that a complete differential diagnosis has been constructed. The second mode is for complex, CPC-type cases in which an extensive patient evaluation has already been done but for which there is no readily apparent diagnosis. Here a user desires diagnostic assistance in determining ways to put the multiple components of a case into logical perspective.

During case analysis, QMR provides several options. In simple cases involving a few positive patient findings, it is likely that at least several diagnoses can individually explain all of the positive findings. After entering the findings of a simple case, the user can indicate, "Examine the single diagnoses explaining all findings." QMR will then list all diagnoses in the QMR knowledge base fully consistent with the positive patient findings entered. All diagnoses explaining all the positive findings are displayed, independent of their prevalences.

Another option, "Review single diagnoses per INTERNIST-1 approach," allows a user to list the most attractive diagnoses based on a quasi-probable rating scheme (see below). An additional QMR option identifies pairs of closely related diagnoses that in combination can explain all of the patient's findings. For the identified pairs, each diagnosis of a given pair explains only a portion of the patient's findings—but together each pair explains all findings.

QMR as a high-level information management utility. The QMR case-analysis mode allows a user to enter up to 95 positive and 95 negative findings (190 total findings) from a case. Positive findings are those present in a patient's case; negative findings consist of pertinent abnormalities looked for but absent in the patient. For complicated CPC-type cases, the user can employ a series of advanced case-analysis functions. QMR utilities exist to generate diagnostic hypotheses of various forms, to allow the user to assert one or more diagnoses as being present in a patient and to then allow QMR to process the residual unexplained findings and critique the strengths and weaknesses of any user-entered hypothesis. After storing a patient case on a disk file, the user can later retrieve the information to add and analyze additional findings.

In complex cases, it is extremely unlikely that any one (or even two) diagnoses will explain all of a patient's findings. To analyze such difficult cases, QMR provides two methods for generating and ranking hypotheses: review of single diagnoses per the INTERNIST-1 approach, and display of possible global case overviews. Ranking hypotheses per the INTERNIST-1 algorithm allows a user to examine the best-rated diagnoses as determined using the quasi-probable INTERNIST-1 scoring scheme.[3] Hypotheses are ranked by the positive predictive values of the observed findings for the diagnoses, the ability of each diagnosis to explain the clinically important findings in a case, the presence of previously asserted (concluded) diagnoses related (by links in the knowledge base) to a hypothesis under consideration and the negative weight (against a diagnosis) due to findings that commonly occur in the illness being absent in a patient.

In complex cases, there are often many disease states simultaneously present in a patient. If the diseases are related to one another (as represented by the disease links in the knowledge base), then the QMR program can also offer global hypotheses that attempt to tie the entire case together. The QMR "global case overviews" option operates under the assumption that a patient has several pathophysiologically related disorders. Each "global overview" represents one of the many possible ways of logically interrelating individual diagnoses to form a more complete picture of a patient's illness.

In the case-analysis mode, a user can request that the QMR program "critique" diagnostic hypotheses suggested by the user. Essentially, after entering pertinent lists of positive and negative patient findings, the user can say, "What about disease X as a possible diagnosis?" where disease X might be any one of the 572 disorders profiled in the QMR knowledge base. The ensuing critique will explain what evidence in the patient's case supports the suggested diagnosis, what clinical case findings are not explained by the diagnosis and which negative case findings are strong evidence against the suggested diagnostic hypothesis. In the critiquing mode, QMR also generates a list of diagnoses related to the user's suggested diagnosis. These related diagnoses merit consider-

ation because they may enhance the attractiveness of the user's suggested diagnosis—the related diagnoses often account for some of the patient findings not directly explained by the user's diagnosis.

During a case analysis, the user can "assert" that a particular diagnosis is present in the patient. The QMR program will then remove all findings explained by the asserted diagnosis from further consideration. This allows the user to reexamine the residual findings in the case in a newly created context. Diseases related to the asserted (concluded) diagnosis are subsequently given extra consideration. Conclusion of a diagnosis is not irreversible; a "retract asserted hypothesis" option provides for change. The "assert a diagnosis" option is helpful in analyzing cases where more than one independent (unrelated) diagnosis coexists in the same patient.

Figure 1 summarizes a study estimating the possible impact of QMR's case-analysis capabilities on the practice of inpatient general internal medicine. Over a six-week period, 36 of 116 patients serially admitted to two general medical wards were deemed by the ward team (attending physician, house staff and students) to present diagnostically significant problems. QMR analysis of those cases was found to be helpful in 72% of the cases.

Future Directions for QMR

The Quick Medical Reference project has provided us with an opportunity to improve on several aspects of the INTERNIST-1 program. QMR has broadened the scope of the project's objectives. INTERNIST-1 provided only a diagnostic consultant capability for complicated case analyses. QMR represents an "information tool" that can serve as an electronic textbook, an intermediate-level consultant or a sophisticated analytic tool. These features extend the capabilities of the original INTERNIST-1 program. In addition, QMR has shown that many of the "expert system" characteristics of the INTERNIST-1 program could be implemented on a microcomputer in a manner that would run at least as fast as the original mainframe version of the INTERNIST-1 program.

The QMR program has so far been under development for only a year. The program and its capabilities are evolving rapidly on several fronts. Projects related to QMR currently planned or in progress include

- Improving the QMR program itself.

The INTERNIST-1/QMR knowledge base will be further completed, tested and refined. The authors estimate that an additional 180 disease profiles must be added to the existing 572 profiles to encompass the breadth of expertise expected of general internists.

The QMR user interface will be improved by adding a "natural language" processing capacity to deal with synonyms for terms in the QMR vocabulary entered by users.

An improved question-generating capability for use during case analysis will be implemented. In addition, a feature to allow users to specify a suggested diagnosis that must be taken into account during case analysis will be developed.

Improved on-line help capabilities and better user training materials will be developed for QMR.

- Incorporating the National Library of Medicine's medical subject heading terms into the INTERNIST-1/QMR knowledge base is a first step in being able to provide relevant literature references regarding diseases and findings. This will also allow investigation of a semiautomated literature review as a means of updating the knowledge base.

- Creating educational applications for the INTERNIST-1/QMR system. QMR itself will be evaluated as a tool for medical education of students and house officers. The Clinical Patient Case Simulator (CPCS) is a mainframe-based program written by one of us (R.A.M.) to construct artificial patient cases from a specialized form of the INTERNIST-1 knowledge base.[21] The artificial patient cases can be used for teaching medical diagnosis. The CPCS will be converted to run on microcomputers in parallel with the QMR knowledge base.

- Evaluating QMR in the future. Studies of QMR's user acceptability, its relevance to clinical practice (see Figure 1) and its effeet on clinical outcomes will be carried out as the program is further developed.

Conclusion

Several important questions remain to be answered regarding medical expert systems. First, is it possible to develop academically oriented, high-quality computerized medical knowledge bases for widespread use? We believe the answer to this question is "yes" but, as described above, the costs in time, money and dedication are substantial. Second, if it is possible to develop such knowledge bases, do practical methods for their maintenance exist? Again, we believe the answer to this question is yes. Unfortunately, the development of semiautomated or fully automated updating techniques for medical knowledge bases is largely unexplored; labor-intensive manual methods are required at present. Third, can diagnostic computer programs become efficient, inexpensive and user friendly enough to compete with the current "gold standard" for diagnostic assistance, a phone call to a respected colleague? It is our opinion that powerful microcomputers now available may eventually provide diagnostic assistance at an affordable cost in time and money. The definitive answer to this question awaits further development and testing of programs like QMR. A fourth question is whether physicians will be willing to use even "perfect" computer programs in routine practice. Few diagnostic programs have reached a stage of development to undergo serious field testing to answer this question. Finally, there are important legal and ethical issues related to the use of computer programs in clinical practice. Should anyone be allowed to use a medical computer program? Who will be held legally liable if the programs give mistaken medical advice? Will the legal "standard of care" come to include the use of medical computer programs, forcing physicians to adopt a new technology? Many such perplexing questions remain to be answered.[22]

Initially QMR was developed to provide rapid and convenient access to the contents of the INTERNIST-1 medical knowledge base. More advanced information-processing capabilities have been added through QMR's case-analysis mode to help work through complicated case problems. As noted above, clinical validation of QMR has not yet been attempted. More detailed studies of the type described in Figure 1 will be required. Thus, QMR cannot be made available to health care professionals on a routine basis at

A prospective evaluation was recently conducted to examine the clinical usefulness of the QMR case-analysis mode in the setting of inpatient general internal medicine. Two of us (M.A.M. and S.M.C.) studied a total of 116 patients consecutively admitted over a 6-week period to two general medicine wards at University of Pittsburgh teaching hospitals. Only cases admitted for diagnostic evaluation were submitted for computer analysis. These included both diagnostic dilemmas and routine problems such as evaluation for anemia. Excluded from QMR analysis were admissions for such purposes as chemotherapy or terminal care where no diagnostic issues were under consideration. A total of 36 out of the 116 cases were subjected to computer analysis. Thus, 80 of the 116 cases were deemed not to be diagnostic problems. The utility of the simple information-retrieval capabilities of QMR—such as providing a disease profile for review purposes—was not evaluated in these 80 patients.

Pertinent historical items, physical findings and laboratory values from each patient case were entered by an experienced QMR user via the program's case-analysis mode. A differential diagnosis list was generated by the computer for each case, with the diagnoses sorted in descending order of likelihood. This ranking was then compared with the differential diagnosis determined by the ward team (attending physician, house staff and medical students) on teaching rounds the day after they had independently completed their own rankings. The final discharge diagnoses, when available, were used to determine the accuracy of the initial impressions of the ward team and the QMR program.

The 2 sets of initial differential diagnoses (ward team's and QMR's) were compared for similarities and differences. In 21 of the 36 patients subjected to computer analysis, the major clinical diagnosis under consideration was the same as the top-ranked QMR-generated diagnosis. For these 21 cases, review of the computer's analysis modified the clinicians' planned approach to the case in 6 instances. In 2 patients, the clinicians reordered their ranking of possible diagnoses after reviewing the QMR differential diagnosis; in 2 patients the clinicians discarded diagnoses they had been considering after reviewing the QMR differential diagnosis and in 2 patients the clinicians added diagnoses suggested by QMR to their working differential diagnoses.

In 15 patients, the ward team's working hypotheses were different from QMR's differential diagnosis. Of these 15 cases, QMR's suggested diagnosis was in fact confirmed at the time of discharge in 3 patients. In 4 of the 15 cases, the final diagnosis remained unknown so no comparison was possible. In these 4 cases computer analysis neither added to nor detracted from the clinical evaluation. In 8 of the 15 cases, the QMR-suggested diagnoses did not match the final discharge diagnoses. In 1 of the 8 cases, both the ward team's and the computer's diagnoses were incorrect. In the remaining 7 patients, the clinicians' diagnoses were accurate and QMR's diagnoses were not appropriate. In 2 of these 7 cases, the diseases under consideration were contained in the knowledge base of QMR, and thus the performance of QMR could be categorized as misleading. In the remaining 5 of the 7 cases where the QMR's diagnoses were in error, a major component of the correct differential diagnosis had not yet been included in the QMR knowledge base. The disease processes not known to the program included osteomyelitis, superior vena cava syndrome and the syndrome of inappropriate antidiuretic hormone secretion occurring as complications of bronchogenic carcinoma and 3 cases with extrinsic spinal cord compression from known neoplastic disease.

In addition to the 5 cases where the major clinical diagnosis under consideration was missing from the QMR differential because of a limited knowledge base, there were 4 other cases analyzed where a complete differential diagnosis was not generated by the computer because of a limited knowledge base in the program. In all 4 cases, the major diagnosis was known to the computer and was given top priority in the QMR differential diagnosis. An important competing diagnosis, however, was not identified because of insufficient knowledge. In 1 of these cases, the computer also added a diagnosis to the clinicians' differential that they had not previously considered.

Overall, when prospectively used to evaluate 36 diagnostically significant patient cases, QMR was deemed to be "very helpful" to the ward team in the management of 12 patients. It added diagnoses in 5 cases, reordered the differential diagnosis in 2 cases, ruled out diagnoses in 2 cases and suggested the correct diagnosis in 3 cases in which the clinicians were incorrect. The QMR analysis was rated "helpful" in an additional 14 patients for whom the program confirmed the ward team's major clinical diagnoses. In 2 cases where the diagnoses remained unknown at the time of discharge, QMR analysis was rated as "unhelpful" or "misleading" by the ward team. In the remaining 8 of the 36 patients, the QMR analysis differed from the validated discharge diagnoses. In these 8 cases, the computer was in error and potentially misleading. In 6 of the 8 cases, however, QMR missed the correct diagnoses because of an insufficient knowledge base rather than an intrinsic error in the medical decision-making system. In summary, in a prospective evaluation of patients consecutively admitted to general medical wards, QMR case analysis was found to be helpful in 26 of 36, or 72% of the diagnostically significant cases. The bulk of the errors in QMR case analysis, moreover, can be attributed to limitations of the knowledge base, which is still under development.

Figure 1.—A prospective evaluation of the potential relevance of Quick Medical Reference (QMR) to inpatient general internal medicine.

this time. After further development and careful testing of its capabilities during the next few years, we hope to release QMR to the general medical community. Its use should help physicians to be more efficient, more reassured and more effective in the diagnosis of problems and in the care of patients.

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The Medical Gopher—A Microcomputer System to Help Find, Organize and Decide About Patient Data

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We have developed a microcomputer-based medical workstation that does some of physicians' "gopher" work of fetching, organizing, reviewing and recording. For two years physicians have used the first version of this system to order all diagnostic tests in a general medicine clinic. They are about to use a newer version to write prescriptions and office visit notes and to find general medical and patient-specific information. Users can enter data into this system by "pointing" with a "mouse" to menu items displayed on a video terminal. In the course of a computer activity, a physician can obtain information about drugs, tests and different diagnoses, as well as about the patient. The microcomputer workstations are linked to each other and to a central hospital information system through a high-speed network link. Our physicians have accepted the initial order-entry system, and early experience suggests they prefer this faster and more sophisticated system.

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Physicians use two kinds of facts: (1) patient facts about symptoms, findings, laboratory results and treatments, and (2) medical facts about drugs, diseases, findings and tests. Physicians spend much of their time seeking, reviewing, organizing and deciding about such facts. For instance, a man has abdominal pain. Has he ever had an upper gastrointestinal series? Look through the old records. What else could cause the pain? Think through the differential diagnosis list. Is he a drinker? Any high amylase levels? Again, search the chart. What are the results of the admission laboratory tests? Call the laboratory. How do today's results compare with yesterday's? Update and review the flow sheet. When considering a treatment, what is an adequate initial dosage? Check the *Physicians' Desk Reference.* There is also paperwork: return-to-work forms, prescriptions, free-from-contagious-disease reports, camp physical examinations, disability forms—just to name a few. The above work is often described as "scut" or "gopher" work.

A computer can help with much of physicians' "gopher" work of finding, reviewing, organizing and deciding. We have shown that a computer-stored medical record system can reduce oversights by reminding physicians of clinical conditions that need attention.[1] In this system, reminders were transmitted on a paper report produced the day before a clinic visit. The computer was not aware of patient complaints or findings, nor a physician's orders recorded at a clinic visit and, thus, could not help with most of the visit-associated gopher work.

To be most helpful, a computer has to obtain information from a physician at a patient's visit. As a first step in that direction, we have installed and tested the effect of feedback from a microcomputer-based test-ordering system. Our physicians have used one of eight clinic microcomputers (IBM XT compatibles) connected to a central hospital computer system to order all diagnostic studies in our general medicine clinic for the past two years. The 200 physicians who have used the system to date find it acceptable, but not preferable, to manual ordering.

To be preferable, we believe that such workstations must be very fast, easy to use, flexible and provide a broad range of clinical services. We have developed a second-generation system, based on an IBM AT (Advanced Technology)-compatible microcomputer—three times faster than the initial machines—to satisfy these four criteria. With this system physi-

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cians and nurses can write progress notes and prescriptions, review patient records and order tests. The computer can fetch, as needed, patient and general medical facts and automatically detect patient conditions and physicians' orders that need special attention. Because it helps with medical "gopher work," we call it the Medical Gopher. In the following, we describe this system as it is now being implemented in a general medicine clinic.

Materials and Methods

Hardware and Software

We designed the system as a network of microcomputers linked to a central institutional computer. The dedication of an individual microcomputer to each user assures quick computer responses and makes possible clinical services that would have been too expensive or too slow on a shared central computer. The current system runs on AT-compatible Zenith Z248 computers.

The program runs under the MS DOS disc operating system. This enables users to run any of their favorite programs on the machine when not using the Medical Gopher services. The programs are written mostly in R-BASIC, a compiled and extended version of the original Dartmouth BASIC from Cosmos, Inc (Seattle).

Mierocomputers are linked to each other and to a file server—a dedicated microcomputer containing 140 million characters of hard disc storage—and to our central Digital Equipment VAX computers through an Ethernet Network (8 million bits per second). The central VAX computers carry electronic medical records for all of the primary care clinics (more than 140,000 patients).[2] The VAX computers also support a full appointment and clinic management system, an inpatient and outpatient pharmacy system and an inpatient and outpatient laboratory system[3] developed by the Regenstrief Institute.

The network file server carries the medical records of the 10,000 most active clinic patients. Any of the microcomputers can immediately call up any of these patient records. As new laboratory and pharmacy data are entered into the VAX computer, data belonging to patients on the network are automatically transferred to the file server. When patients whose records are not on the file server present for service, their records are sent from the VAX to the network. Network records of patients whose records have been inactive for a fixed period of time are purged at intervals. A patient's entire medical record is copied from the file server to the microcomputer's random-access memory whenever a physician references that patient and is immediately available for physician review, automatic decision assistance or both.

AT microcomputers are not cheap. A Z248 with a 20-megabyte hard disc and a network interface costs about $3,000 discounted. But with the availability of reduced AT chip sets (R. Glitman, "New Chips to Cut PC Size and Price," *PC Week*, 1986; 3:1+), discless AT workstations could soon sell for from $600 to $700.

Flexibility

Data-Base Manager

Because the information needs of practices and practitioners change over time, medical information systems must be flexible. One way to obtain flexibility is to base a computer application on a data-base management system. The Medical Gopher is based on the Revelation data-base management system (Cosmos, Inc), an imitation of the PICK operating system that, like the MUMPS language, stores numeric text as ASCII characters and allows records and data items to vary in length. Data-base systems with variable-length records and data elements are more adaptable than those requiring fixed lengths. For example, they can accommodate the new nine-digit ZIP codes mixed together with the old five-digit ZIP codes, and they can accept various amounts of free text in any record.

Data-base systems generally provide query and report-writing capabilities. This feature lets a user ask ad hoc questions, such as, "which patients are taking Zomax [zomepirac sodium]?"—a useful question to ask when Zomax was removed from the market a few years back. In Revelation, the command would be "LIST PATIENT ID. NUMBER WITH RX = "ZOMAX." Revelation also has facilities for eounting and summing the contents of selected fields within records of interest, and it can produce reports sorted aecording to the value of any of its data elements. For instance, patients can be listed in order by attending physician and, within the attending physician lists, by hospital number.

For the flexibility of a data base, a small price is paid in performance. But the cost is rarely consequential in this era of inexpensive hardware.

Extended Reporting

The Medical Gopher extends the report capability that comes with the data-base system. A practiee ean construct reports made up of data from a patient's medical record or from any of the assoeiated files. A user has full control of the format of these reports, including the position of its fixed and variable components, the use of underlining, bold and italies and the content of headers and footers. Computed variables, such as the Framingham Risk or reminders, based on CARE rules (see below), can also be included in such reports. The computer can produce reports on demand for individual patients or in batch mode for many patients, such as the patients with scheduled appointments for the next day. Batch reports can be printed in any prescribed order. For example, address labels can be produced that are sorted by ZIP code or an alphabetic listing of the patient registry can be done that includes the name, address and telephone number, sorted by attending physician. Reports can be simple, such as for specimen labels, or complicated, such as visit notes.

Free Text Versus Codes

A practice faces a trade-off between storing information as coded entries or as free text. Coding saves storage space and permits a computer to use the stored data more intelligently. When the number of possible entries is few, as is the case for sex (male/female), coding comes as a "free" by-product of menu selection. When information is complex, however, as is true for most medical narrative, eoding requires much more training, is more subject to errors and is more time consuming than direct text entry.

The Medical Gopher takes a flexible approaeh to this issue. It permits mixing of codes and free text within any particular data element. As many as 64,000 characters of text comment—the equivalent of 25 single-spaced typed

pages—can be substituted for, or appended to, an entered code.

Word processing capabilities are provided to modify text entry. The cursor control keys on the microcomputer have their expected meanings. Words that do not fit on a single line are automatically moved down ("word-wrapped") to the next line when there is insufficient space to complete a word on the current line.

Ease of Use

The success of a computer system intended for physician use depends on how easy it is to use. The following features are examples of approaches that make systems easier to use.

Mice and Menus

The Medical Gopher is "menu oriented." This means that most of the computer's questions can be answered by selecting an item from a computer-printed menu. In the initial system, menu items were selected by typing in the item number.

A mouse is a device the size of a cigarette package with one to three buttons on its top surface. When a user moves the mouse in any direction on a table top, the cursor "pointer" moves in the same direction and a proportional distance on the video screen. Mouse selection—that is, pointing the mouse cursor at a menu item and clicking a button—is faster than most other selection techniques.[4] The Medical Gopher permits data entry by mouse selection.

Numbers such as dates, test results and patient identifiers can also be entered by the mouse. When a user reaches a numeric field, the Medical Gopher "paints" a numeric keypad on the screen (Figure 1). The user can enter a series of one or more digits by "pointing" the mouse cursor to the appropriate numeric key and clicking the left mouse button.

Form Orientation

Gopher video displays are form oriented. This means a fixed form, such as shown in Figure 1, is painted on a screen and a user moves from question to question as he or she would when filling out a paper form. Form orientation lets a user take advantage of positional cues that are important to user orientation.[5] At any point in a form, the user can obtain help about how to answer the current question by pressing a special key. Messages about erroneous entries appear spontaneously. Both help and error messages appear at the bottom part of the form. Figure 2 shows the message displayed when a user asks for help in entering data into the author field on the reference form.

All application screens have a similar look and use the same conventions to make it easy to learn the system.

Data-Entry Shortcuts

A "default" is an answer the computer presents to a user as a "guess" about what the user intends to enter. The user can accept the default by pressing the return key. In the Medical Gopher, defaults can be conditional on data entered in other parts of the form. For example, the default "prescription Sig" depends on the drug entered in the preceding field. For Cafergot,* the "Sig" would be:

Take two tablets when headaches begin, then one tablet every half hour for a total of four dosages. Take no more than six tablets per day, no more than ten per week.

Defaults, obviously, can save keystrokes.

There are also shortcuts for entering dates and times. A user can enter "T" to tell the computer to store today's date, "T−5" to tell it to enter the date five days ago and so on. The corresponding abbreviation for the time of day is "N."

Names and Numbers

The Medical Gopher accepts names almost everywhere a human would. Diagnoses, physicians, procedures, clinics, patients, tests and drugs can all be identified by name and by their assigned number. If a user is not certain of the spelling of a name, he or she can type the first few letters and the computer responds with a menu showing names beginning with the entered letters.

In keeping with the name orientation, the system also permits synonyms or aliases for patients, tests, drugs, locations, physicians and so on. Synonyms have many uses. They can be used to equate brand with generic drug names or to access a patient's record by either her married or maiden name.

Avoiding Errors

Errors create problems that make systems difficult to use. Computer science offers numerous techniques for verifying entered data.[6] Of these, the Medical Gopher uses pattern

*A combination product, each tablet of which contains ergotamine tartrate, 1 mg, and caffeine, 100 mg.

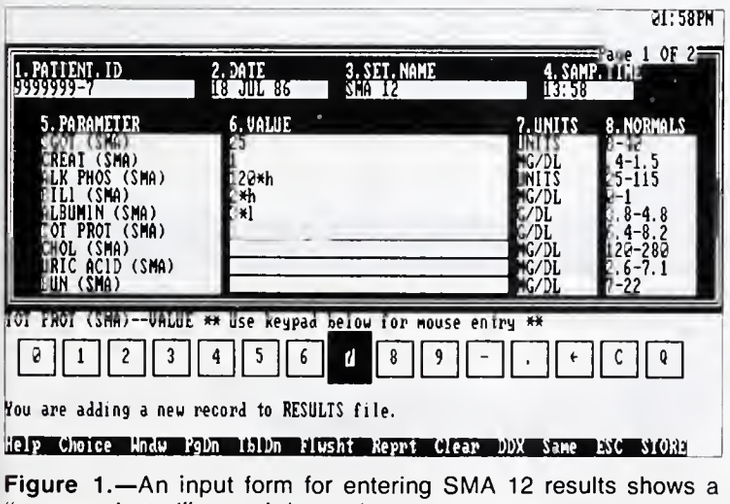

Figure 1.—An input form for entering SMA 12 results shows a "mouse-oriented" numeric keypad.

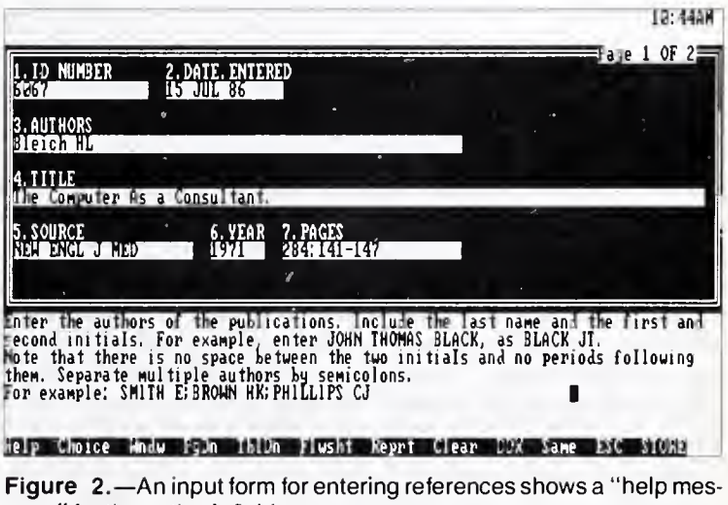

Figure 2.—An input form for entering references shows a "help message" for the author's field.

matches, range checks and check digits. Pattern matches apply to data elements such as telephone numbers, which have standard patterns—that is, three digits, a dash and then four digits. Range checks apply to numeric observations, dates and times. The Medical Gopher applies three different range checks. It forbids entries outside of the absolute range, requires confirmation for results outside of the critical range and flags results outside of the normal range.

Check digits are the extra digits added to identifying numbers to detect common typographic errors. The standard MOD 10 check digit reduces errors by an order of magnitude. Check digits are particularly important to patient identifying numbers because they protect against the dangerous error of entering one patient's data in another patient's record.

Finding and Reviewing Patient Data

The Medical Gopher provides a number of "gopher" services. It carries information about patient demographics, visits, symptoms, findings, tests and treatments—a minimedical record, if you will. The computer helps a physician find, organize and review this patient information. A major assist to finding and reviewing patient data is the flow sheet.[7] Figure 3 shows the questions a physician answers to tailor a flow sheet to a particular purpose. Flow sheets are predefined for common problems, such as diabetes mellitus and weight loss, and organ systems, such as liver and heart, as shown on the menu of Figure 3. The users can create their own flow sheets on demand by selecting several items from a flow-sheet menu or by typing in the names of any of 3,000 observations or observation classes defined within the system dictionary. For example, a flow sheet can be created of drug usage and body temperature to identify drug therapy that was initiated just before the new occurrence of a fever, or a flow sheet can show diuretic use, electrolytes and heart size by chest x-ray film (Figure 4). The computer highlights abnormal results with bold print. (This highlighting, however, does not show up on the printed versions of the screens that appear in the figures.) A user can tailor flow sheets further by constraining their time window, such as to the time since the last visit, and the degree of abnormality, such as to measurements that show an abnormality.

A user can choose among alternative flow-sheet formats. Figure 5 shows a compressed version of the flow sheet shown in Figure 4. In this flow sheet, results are displayed as single letter codes and time is displayed on a uniform axis.

Flow sheets can be obtained during the course of other gopher services, such as prescription or order writing. Pressing a single key tells the computer to interrupt the current activity with the flow-sheet specification form. When the user finishes reviewing the specified flow sheet, the computer returns instantly to the place in the previous activity where the user was working. The ability to interrupt and then resume a process without losing partially completed work applies to most of the Medical Gopher services.

The computer will also find and display information in more traditional formats. For example, visit notes can be reviewed, as shown in Figure 6. Other traditional formats, such as prescriptions, letters to consulting physicians and back-to-work notes are also available.

A user can develop his or her own forms to gather data from various parts of the Medical Gopher data base for a particular purpose. A letter to a referring physician ean be created by selecting information from the prescription file, laboratory results file, initial history and physical record and combining it with newly entered narrative text to create a consultant's report. The computer, thereby, saves much of the work of finding and transcribing information required with manual systems.

Deciding About Patient Data

The Medical Gopher also helps with the process of deciding about a patient. Physicians can write protoeols (CARE rules)[8] that generate new variables or reminders on the basis of raw data stored in a patient's medical record. For example, a CARE rule could calculate the Framingham Risk of cardiovascular disease, based on algebraic combinations of raw data such as age, last cholesterol level or blood pressure measurement, or it could remind that a patient's annual flu shot is due based on the patient's age, problem list and the current date. Figure 7 shows the CARE rule that computes the Framingham Risk CARE rule for women. The user creates a CARE rule by answering a series of questions on an input form. More complicated CARE rules can be created by combining other rules algebraically or logically.

CARE rules can be initiated by many "stimuli." By command, a user can initiate a set of CARE rules while reviewing a patient's record. It takes about a second to review the rules for preventive care and determine whether a patient needs

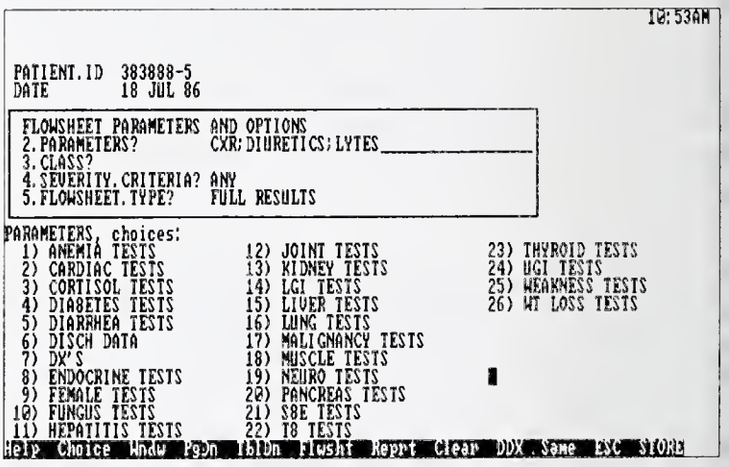

Figure 3.—The subform used to specify particular flow sheets is shown. A menu of predefined parameter sets is displayed below.

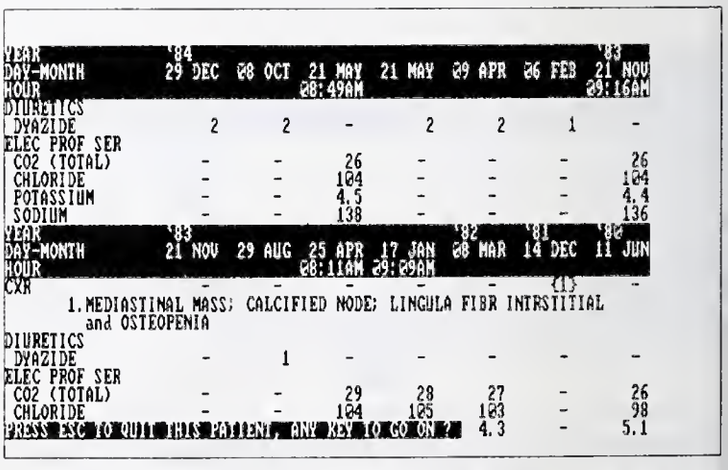

Figure 4.—Part of the standard flow sheet defined by the user in Figure 3 is shown.

mammography, cervical Pap testing, occult blood testing, an influenza vaccine or pneumonia vaccine.

The names of CARE rules can be embedded in report definitions. In this case, the CARE rule is executed when the report is printed. The value of a CARE rule can be included in any patient-oriented report.

CARE rules can also be executed in batch mode. In this case, the results of the execution are saved in a computer file for later use. In the late summer, this mode could be used to identify patients eligible for influenza vaccinations and the output of this batch "retrieval" could generate personalized letters that invite patients to schedule a visit for a flu shot in the early fall. Batch retrievals can also obtain data for clinical or management research or both.[9]

Finally, CARE rules can be stored as attributes of tests or treatments. In this case, the rules are executed when data for the associated test or treatment are entered into the computer. In this mode, the rules call attention to a dangerous condition as soon as the condition is recognized, rather than waiting for the patient's next visit.

The computer can help a physician decide about a patient's data in yet another way. It can tightly summarize the patient's record by organizing abnormalities according to their common possible causes (see Figure 8). This makes it easy to identify abnormalities that have not yet been explained and to review evidence for and against the causes of known abnormalities.

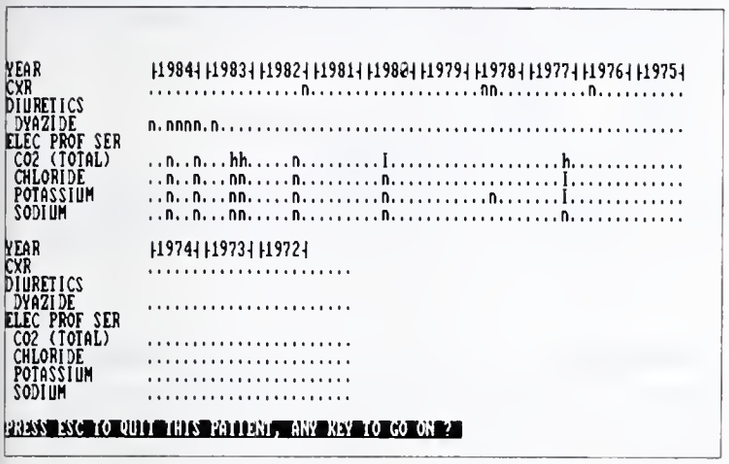

Figure 5.—This is a compressed version of the flow sheet shown in Figure 4.

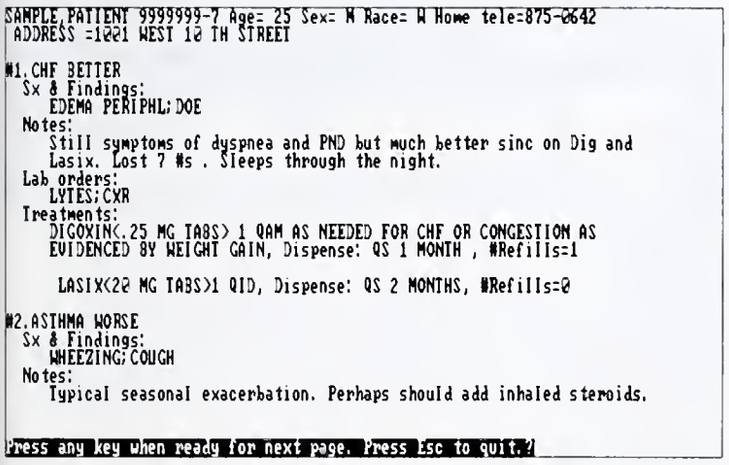

Figure 6.—A portion of a visit note is displayed on the video screen.

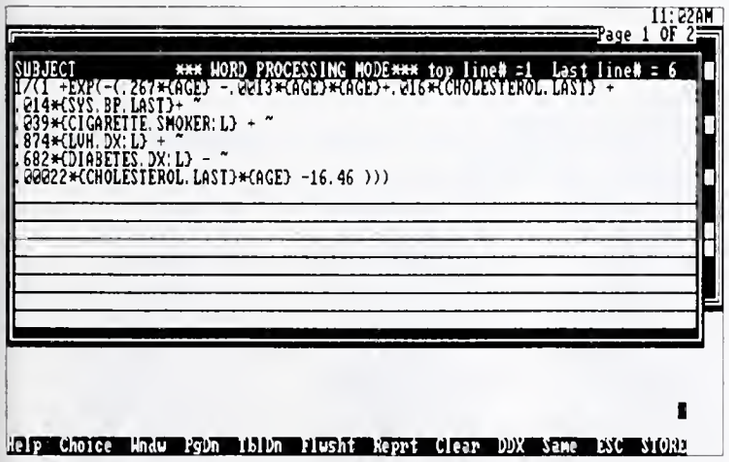

Figure 7.—The CARE rule definition for a woman's Framingham Risk. The input window has been expanded to display the entire RISK function.

Finding and Deciding About Medical Facts

The Medical Gopher assists the performance of many routine management activities, including order, prescription and progress-note writing. In the course of these activities, the computer eliminates the work of finding some general medical facts. For example, when a physician is deciding about treatments for a given problem, the computer displays the common treatments in a menu. If the doses and "Sigs" of the prescription(s) presented in these menus are acceptable to the physician, he or she can complete a prescription by a single menu selection. If the details of these prescriptions are not acceptable or if the physician wants to write a prescription not listed in the menu, the computer provides facts about the drug of interest—for instance, the list of dosage forms for a drug—as the physician writes the prescription. Similarly, when a physician writes diagnostic orders for a particular problem, the computer displays the usual workup for that problem. Thus, needed tests can be ordered by menu selection. Finally, when a problem is described, the computer displays a list of questions about the quality, intensity, timing and other dimensions, each of which includes problem-specific menus (see Figure 9). The lower part of Figure 9 shows the narrative into which the computer converts this input.

The computer also helps the decisions associated with order writing. It detects drug-drug, drug-test and drug-diagnosis interactions. Drug-diagnosis interactions take into account a diagnosis that can be inferred from the raw data in the

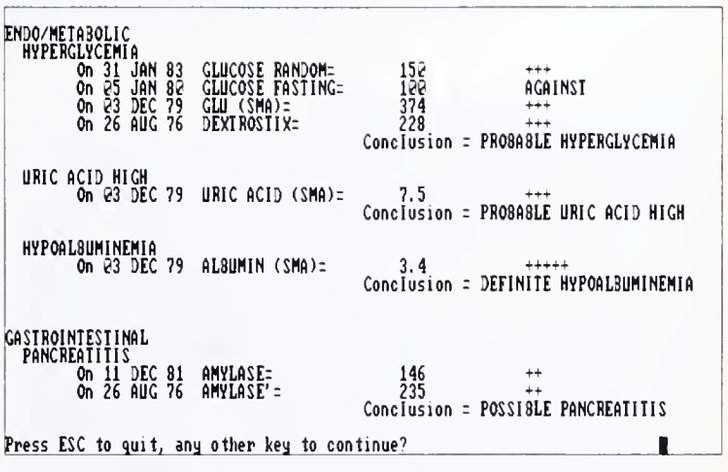

Figure 8.—A portion of the summary analysis of a sample patient's record is shown.

electronic medical record, as well as those explicitly recorded in the problem list. A message is produced when propranolol hydrochloride is prescribed for a patient with congestive heart failure or asthma. By pressing the "Help" key, the user can obtain additional information about the interaction (Figure 10).

On command, a physician or nurse can obtain additional medical facts, such as descriptive information about tests, drugs, diagnoses or findings.

Information about differential diagnoses is also available. On command, a user can review the possible causes of current patient findings. If more than one finding is entered, the computer lists the diagnoses that explain all of the entered findings. Possible causes that have particular relevance to the patient under review are highlighted. For example, in Figure 11, which shows half of the list of possible causes, the computer highlights renal failure and phenytoin because the patient has a high blood urea nitrogen level and is currently taking phenytoin. The highlighted causes are those to be considered first when trying to explain a particular symptom in a patient. The user can also obtain supporting references and discussions on each of the listed causes.

Other Practice Services

The Medical Gopher helps physicians complete tasks that are not patient related. For example, a physician can record the author, title, source and comments about each of his or her favorite references. These references can then be retrieved by author name, source or key word within a title.

The computer assists telephone management. It provides access to an electronic file that contains telephone numbers and addresses of professional and business colleagues. It also maintains a log of patient telephone messages. Each entry includes the patient name and telephone number, as well as the purpose and the urgency of the call. The physician can go through all of the calls at the end of a day and command the computer to dial each patient as the physician proceeds through the telephone message log. While in the same form, the physician could write prescriptions, order tests, review differential diagnoses or any of the other functions described above and then return to his or her place in the telephone log to process the next message.

Telephone management also touches the bibliographic file systems. Users can dial up the BRS (Bibliographic Retrieval Services, New York) data base and retrieve articles from the National Library of Medicine file into their local bibliographic file.

Experience and Conclusions

As mentioned in the introduction, we have used a version of the Medical Gopher system in a general medical clinic at Wishard Memorial Hospital (Indianapolis) for more than two years. During this time physicians had access only to the order-entry features of the system. Entry was by keyboard—the mouse was not yet available. Physicians used this system to request all diagnostic studies, including x-ray films, laboratory tests, nuclear medicine and orders in the clinic. But it took a physician an average of 30 seconds to order each test—longer than manual test ordering. When using this initial workstation, physicians accepted but did not prefer computer order entry over manual order writing. We are optimistic that when the new version of the system—three times faster than the old one and with far greater capabilities—is installed, physicians will prefer the computer over manual methods. But if current microcomputers are not fast enough or if current data-entry methods are not easy enough to use, the next generation of technology will be. The third-generation Intel microcomputer chip (on 80386), soon to be available, is three times faster than the chip in the IBM AT. The technology for

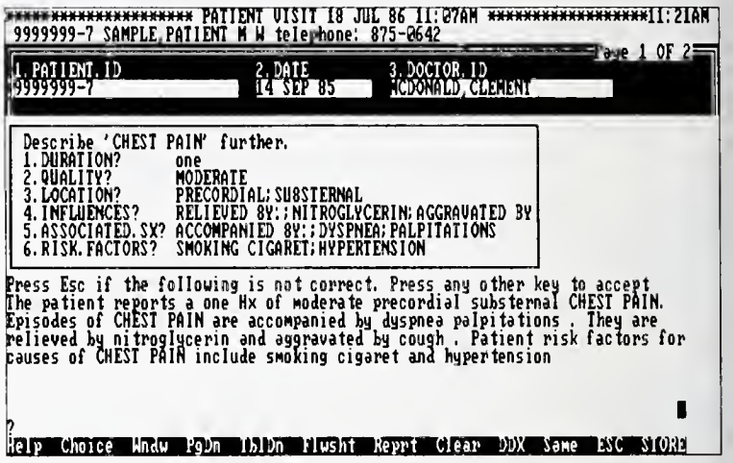

Figure 9.—A subform is used to describe a medical problem, in this case chest pain. The items in the form are entered by menu selection. The computer translates it into the free text appearing below the input window.

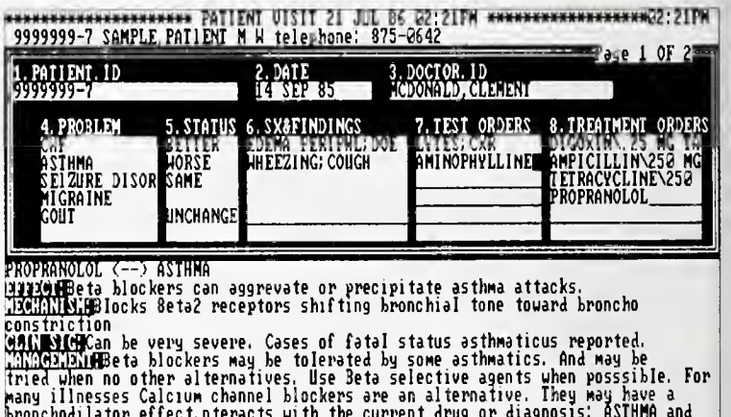

Figure 10.—The visit input form shows the descriptive message that appears when an interaction between propranolol hydrochloride therapy and asthma is detected.

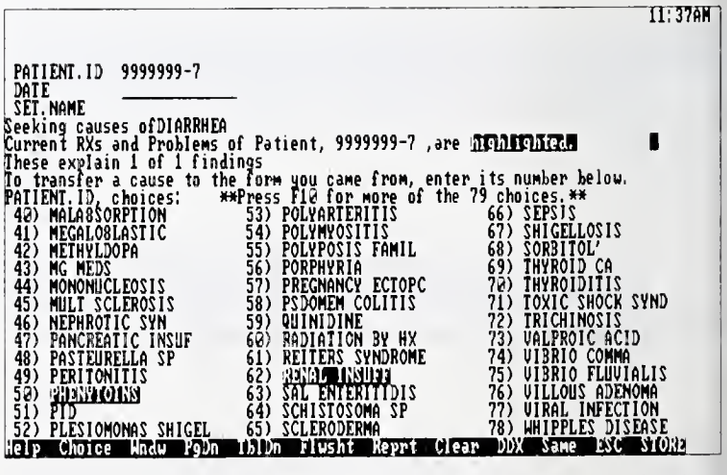

Figure 11.—Part of the differential diagnosis list is shown for diarrhea, with two—renal insufficiency and phenytoin use—highlighted (boldface).

computer interpretation of voice input is rapidly improving.[10] Moderately priced voice boards that understand continuous speech in limited contexts are available now. With the ripening of voice-input technology, physicians will be able to speak their orders to a computer.

We anticipate that within the next three to five years, medical workstations such as the one described in this paper or the ONCOCIN system[11] will be as popular with physicians and nurses as computer-aided-design workstations are now with engineers.

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Medical Expert Systems—Knowledge Tools for Physicians

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Recent advances in the field of artificial intelligence have led to the emergence of expert systems, *computational tools designed to capture and make available the knowledge of experts in a field. Although much of the underlying technology available today is derived from basic research on biomedical advice systems during the 1970s, medical application packages are thus far generally unavailable from the young artificial intelligence industry. Medical expert systems will begin to appear, however, as researchers in medical artificial intelligence continue to make progress in key areas such as knowledge acquisition, model-based reasoning and system integration for clinical environments. It is accordingly important for physicians to understand the current state of such research and the theoretic and logistic barriers that remain before useful systems can be made available. One experimental system, ONCOCIN, provides a glimpse of the kinds of knowledge-based tools that will someday be available to physicians.*

(Shortliffe EH: Medical expert systems—Knowledge tools for physicians, *In* Medical informatics [Special Issue]. West J Med 1986 Dec; 145:830-839)

It was recognized in the early days of the computer age that our modern computational marvels, originally conceived as high-performance mathematical calculators, could be adapted to manipulate text and symbols as well as numbers. Thus computers became viewed as tools for storing and retrieving information, and their use as machines for decision support became a focus of research and development. Accepted tools such as MEDLINE later showed that medicine could benefit significantly from such work.

In the late 1950s scientists first began to suggest that computers might someday play a more active role in helping medical personnel reach decisions about diagnosis and patient management.[1] Instead of viewing computers merely as information sources—rather like electronic textbooks—or as tools for assisting with statistical analysis of large patient data bases, researchers suggested that computers could actually use such information, plus observational data about a patient, to generate individually tailored advice for a specific medical problem. For much of the next 20 years, the focus of such work was mathematical, emphasizing probabilistic reasoning and statistical pattern recognition.[2] In the early 1970s, however, several research groups argued that expert physicians make high-quality decisions without formal numerical analysis and that there must be symbolic or conceptual methods suitable for modeling expert decision making when problems are ill-structured or when formal statistical data are scarce or difficult to acquire. They accordingly turned for research ideas to studies of human problem solving and to the area of computer science with the closest ties to psychology, namely, the field of artificial intelligence (AI).

AI had been born in 1956 at a meeting at Dartmouth College (Hanover, NH) where leading computer scientists first articulated notions of machine intelligence. Alan Turing, the famed British mathematician, had suggested an operational definition for computer-based "intelligent behavior,"[3] but it was at the Dartmouth conference that computer scientists first decided to begin active research in the area. The subsequent early work emphasized the development of general problem-solving techniques and, by 1970, AI was epitomized by analyses and implementation of humanlike reasoning strategies, or heuristics, for focusing attention when solving problems and for maintaining efficient search through a range of possibilities.

Two pieces of work in the late 1960s provided insights

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ABBREVIATIONS USED IN TEXT
AI = artificial intelligence
PIP = Present Illness Program

that are credited with a paradigm shift in AI research during the following decade. These were MACSYMA,[4] a system to help mathematicians solve complex calculus problems involving symbolic integration, and DENDRAL,[5] a program to help chemists identify unknown compounds from their mass spectral data. These systems differed from earlier AI work in that their power and utility were derived principally from their knowledge of a technical domain—that is, from the fields of expertise of the mathematicians and chemists who helped build them—rather than from a powerful generalized inference technique. The recognition that intelligent behavior by computers would depend on the effective encoding of large amounts of complex knowledge left AI researchers poised, in the early 1970s, to work in fields with an inherent emphasis on the use of expert-level knowledge. Medicine provided a natural focus for such investigations.

What Is an Expert System?

Four experimental systems are generally regarded as having started the research field of artificial intelligence in medicine.[6,7] These were MYCIN, a program to advise physicians on antimicrobial selection for patients with bacteremia or meningitis[8,9]; the Present Illness Program (PIP), a system that gathered data and generated hypotheses about disease processes in patients with renal disease[10]; INTERNIST-1, a large system to assist with diagnosing complex problems in general internal medicine,[11] and CASNET, an ophthalmology advisor designed to assess disease states and to recommend management for patients with glaucoma.[12] All four drew on AI techniques, emphasizing the encoding of large amounts of specialized medical knowledge acquired from the clinical literature and from expert collaborators. None used classical statistical techniques, nor did they base their advice on interpretations of accumulated experience in patient data banks. On the other hand, each was influenced by earlier AI work on general problem-solving techniques, and two of the systems (PIP and INTERNIST-1) explicitly modeled hypotheticodeductive behavior,[13,14] the familiar process by which physicians formulate tentative hypotheses rapidly after obtaining the first few pieces of information about a patient and then let those hypotheses (typically a differential diagnosis) guide further data collection and problem solving.

It was this handful of medical systems, plus a geology advisor known as PROSPECTOR,[15] that led to a growing interest in AI systems that might function as expert consultants. By the late 1970s such systems had become known as "knowledge-based systems" or "expert systems," terms that continue in common use. Thus, the term "expert system" originally implied a computer-based consultation system using AI techniques to emulate the decision-making behavior of an expert in a specialized, knowledge-intensive field.[16] The term has subsequently been broadened as the field has been popularized, so that an expert system's roots in artificial intelligence research can no longer always be presumed. There are arguments for calling *any* decision support system an expert system if it is designed to give expert-level problem-specific advice, even if the underlying programming and analytic techniques differ from the knowledge-based methods developed by AI researchers.

The explosive popularity of the expert systems notion has moved much of the applied work in this field from university research laboratories to the scores of software companies that have emerged in a fledgling industry since 1980. The successes of the technology have been sufficient to attract the interest of many of the major corporations in the country, several of which have invested heavily in start-up AI companies or have sought to develop in-house expertise in the field. The demand for trained AI scientists has skyrocketed, and one financial observer group has predicted total US spending on expert systems at $150 million in 1986, rising to more than $200 million annually within two years (The Yankee Group, quoted in *Expert Systems User*, vol 2, No. 5, August 1986, p 3). Several new journals and trade magazines have appeared, and the American Association for Artificial Intelligence has grown to a membership of more than 12,000 since its inception in 1979.

Most expert systems developed by the young artificial intelligence industry are used internally within the investing companies. The new technology has generally been used to gather experiential knowledge that had previously resisted efforts to encode it using conventional programming techniques. Examples of successful expert system applications in industrial settings include

- A program that assists with the design of a physical layout for computing components assembled within a metal cabinet.
- A system that assists in the interpretation of soil samples recovered from drilling sites during oil exploration.
- A financial management advisor to assist stock brokers.
- Systems to assist in fault diagnosis for items as diverse as electronic circuits, automobiles and steam locomotives.

It is ironic that a field that owes much of its history to research in medical computing should have grown to commercial viability in industrial settings, whereas the AI companies have thus far largely avoided the medical marketplace. By 1985 only three medical expert systems were being used routinely in clinical settings.[17-19] Of these, only one was a commercial product[18] and two functioned without requiring direct use by physicians.[17,18] (A related program is the University of Utah's HELP system,[20] a hospital information system that incorporates decision-support functions by using a representation scheme and reasoning mechanisms with similarities to those in the expert systems cited.)

Although many of the reasons for this phenomenon are logistic or sociologic, most are inherently scientific and have to do with the complex issues that arise when conventional expert system techniques are applied to high-stakes medical problems about which knowledge is still limited, physiologic models are incomplete and the uncertainty in both associations and interpreting data is severe.

Research Perspectives in Medical Artificial Intelligence

For purposes of the following discussion, an expert system will be assumed to be a consultation system that uses AI techniques for encoding knowledge and solving problems

with that knowledge. The key AI notions in such systems are as follows:

- Symbolic rather than numeric representations of pertinent knowledge from the domain (field) of application.
- General problem-solving procedures for using knowledge stored in accordance with the prescribed conventions.
- Both general and domain-specific heuristics, or rules of thumb, for limiting search and for dealing with areas in which knowledge is limited or missing.
- Schemes, either numeric or categoric (algorithmic), for dealing with the uncertainty in the domain.

The following sections outline several of the key research and conceptual topics in medical AI research. Because the AI notions listed above may not be familiar to physicians, they are clarified with medical examples at appropriate points within the text.

Knowledge and Heuristics

The distinction between "data" and "knowledge" is generally emphasized in expert systems work. Computer data bases are a familiar concept—that is, collections of individual observations or data points; what, then, is a computer knowledge base? First, factual knowledge tends to be drawn from analyzing data. As such, it is frequently subject to controversy and colored by personal experiences. All physicians are familiar with scientific debates about how a given set of data ought to be interpreted; the 1970s controversy regarding oral hypoglycemic agents after the University Group Diabetes Project reported its results is only one such example. A computer data base might record the observation that "Mr John Jones had a blood pressure of 180/110 mm of mercury on August 3 and a myocardial infarction on September 15." On the other hand, a knowledge base that included information derived from analyzing observational data in a data base might record the *fact* that hypertension is associated with an increased risk of coronary artery disease.

Not all knowledge comprises factual associations of this type, however, and intelligent behavior relies in large part on other categories of knowledge. For example, shared knowledge of the world often provides a background of common sense, definitions and assumptions that hardly seem worth mentioning in normal conversation but which must be explicitly encoded in a computer if its behavior is to be appropriate. Consider, for example, the common-sense knowledge that only women can be pregnant, or the assumption that seriously ill patients are more likely to do well if they are admitted to hospital. We generally do not quote data to support such knowledge; the statements are assumed to be widely accepted as true and hardly need to be defended.

Another category of knowledge is experience-based heuristics, or "rules of thumb." Such knowledge is often rather personal, although it can be taught. For example, there is a common heuristic that it is wise to insert an intravenous line early when evaluating an acutely ill patient in an emergency room. The line can always be removed if not needed, but can be indispensable if a patient's condition deteriorates quickly. Matters of personal and professional style also often have a heuristic character to them—for example, the notion that it is wise to build rapport by conversing with an anxious patient before proceeding to the physical examination.

Fortunately there is also a growing number of medical topics for which we have excellent scientific (mechanistic) models that explain aspects of both normal behavior and disease. Such models can be crucial for expert problem solving because they provide a basis for reasoning from first principles when a patient presents with an unusual diagnostic problem or a difficult management dilemma. Such models can be qualitative ("Insulin controls blood sugar levels by regulating the uptake of glucose by cells") or quantitative ("Bicarbonate may be determined from pH and partial carbon dioxide pressure using the Henderson-Hasselbalch equation"). When an expert system functions in a domain for which good models exist, its performance may be greatly enhanced if such information is encoded in its knowledge base.

Symbolic Representation of Knowledge

Although a number of schemes have been used to represent expert knowledge symbolically in a computer, the rule-based approach is perhaps the most widespread and straightforward. Other representation methods can be studied in any of the several excellent textbooks on artificial intelligence.[21,22] Rules are conditional "if-then" statements that indicate circumstances under which conclusions can be drawn or actions taken. Rules can be categorized in several ways, but for illustrative purposes it is useful to think of four major types:

- *Definitional*—for instance, "*If* a patient is male, *then* the patient is not pregnant or lactating."
- *Cause-to-effect*—for instance, "*If* there is an elevation in the serum parathormone level and the patient has normal renal function, *then* anticipate decreased urinary calcium and increased urinary phosphate levels."
- *Effect-to-cause*—for instance, "*If* a patient has recurrent calcium oxalate kidney stones, *then* consider the diagnosis of primary hyperparathyroidism."
- *Associational*—for instance, "*If* a patient has Gram-negative sepsis and has been seriously burned, *then* the offending organism may be *Pseudomonas aeruginosa.*"

Note that an associational rule tends to describe a relationship for which detailed causal mechanisms are not well understood; much medical knowledge is of this type. In addition, only the first of the four sample rules shown allows a conclusion to be reached with certainty (a so-called categorical rule). The others all lend evidence to a conclusion but do not provide definitive proof. Thus, it is sometimes necessary for the knowledge represented in expert systems to include indications of the degree of certainty associated with the relationship described. AI researchers have experimented with a variety of techniques for dealing with weights of evidence.[23] These vary from classic probabilistic measures and the use of Bayes's theorem, to ad hoc scoring schemes and even to efforts to avoid numeric weights altogether.

Rules such as those just described may be encoded in a computer's memory using any of a number of programming languages. The most commonly used for AI work have been LISP and, more recently, PROLOG. Unlike traditional programming languages like FORTRAN, LISP and PROLOG have been designed more for their ability to express logical relationships and to manipulate symbols than for an ability to compute numbers.

Reasoning With Symbolic Knowledge

Encoding knowledge in a computer serves no purpose if it cannot be retrieved and applied effectively. Much of the work in artificial intelligence has therefore focused on how to access and use knowledge that is stored in large and detailed knowledge bases. As previously mentioned, psychological studies have been influential in this work because of the recognition that human beings have a remarkable ability to select and apply relevant knowledge from the vast amount of information they have acquired over a lifetime. People have developed effective search heuristics for quickly focusing on pertinent facts while avoiding tangential considerations; we obviously do not sequentially consider everything we know until we discover a fact that applies to a given problem.

Reasoning methods in AI systems are frequently placed in one of three categories: goal-directed (also called backward chaining), data directed (also called forward chaining) and hypothesis-directed.[24] In a goal-directed system, rules are selected for consideration because of what they might conclude (if true) that is relevant to a diagnostic or management problem—that is, because of the "then" portion of the rule. For example, if a system needed to identify an organism, it might select for consideration the sample associational rule shown earlier. In a data-directed system, rules are selected for consideration because they use information that has become available about a problem—that is, because of the "if" portion of the rule. For example, if a physician reports that a patient has a calcium oxalate kidney stone, a data-directed system might then invoke the sample effect-to-cause rule and add hyperparathyroidism to the differential diagnosis. A hypothesis-directed system, the type that most closely mimics the hypotheticodeductive behavior mentioned earlier, begins with a data-directed invocation of initial hypotheses but then selects additional rules for consideration based on the set of active hypotheses. This notion is similar to letting a differential diagnosis for a case guide subsequent data collection, which in turn allows the diagnostic hypothesis list to be refined.

In recent years system designers have often sought to avoid the constraints of being committed to any single problem-solving technique. One method for doing such "opportunistic reasoning" has been the notion of a "blackboard model"—a working area in a computer's memory that captures the full scope of a problem and allows the problem-solving mechanism to select whichever reasoning technique and knowledge source are more likely to be useful at a given point. The ONCOCIN system described below uses another type of mixed reasoning strategy. More complete discussions of the alternate approaches can be found in sources such as the three-volume *Handbook of Artificial Intelligence*.[25]

Acquiring and Encoding the Knowledge

Exclusively focusing on representing knowledge and using it within a computer would ignore a key additional issue—how the knowledge for a system is acquired and formulated. It is in this area that much of the expert systems "mystique" has evolved. Persons who work with experts to structure and encode their knowledge of a domain have been dubbed "knowledge engineers." There is little doubt that the process of mapping the ill-structured knowledge of a domain such as a medical subspecialty into a form suitable for machine encoding is among the most difficult and time-consuming parts of the expert system building process. Not only must knowledge engineers be familiar with the technical details of the computational tools available, but they must also be willing to make a major commitment to learning enough about the technical domain of an expert so that discussions of sample problems can be substantive and detailed. It is a special breed of programmer who is able to facilitate this transformation of key elements of expertise from a collaborator's mind to a computer knowledge base.

In recent years the knowledge engineering "bottleneck" in expert systems development has encouraged researchers to develop prototype tools that permit experts to "teach" a computer directly about their specialties. The earliest work of this type was a system named TEIRESIAS that allowed infectious disease experts to update and edit the knowledge base for the MYCIN system by critiquing MYCIN's performance on sample cases and entering in English either new rules or modifications to old ones.[26] More recent work on knowledge acquisition has been exploring the use of graphical techniques for defining knowledge. Diagrams on a computer screen, coupled with manually controlled interactive mechanisms—such as touch screens, light pens or "mouse" pointing devices*—can be made intuitive, permitting experts to outline their knowledge without doing extensive keyboard typing.

Model-Based Reasoning

As was mentioned earlier, medical research is increasingly providing us with mechanistic explanations for phenomena that were once poorly understood. As we gain greater insight into why and how the body works the way it does, experts increasingly use such mechanistic knowledge in reaching decisions, especially when reasoning from first principles to develop creative solutions to unusual or aberrant problems. If computer-based systems lack such knowledge and the ability to use it, their performance is inherently limited. The encoding and use of causal knowledge has accordingly become an area of emphasis in medical AI research.[27,28] Although mathematical modeling has involved medical informatics researchers for several decades, the use of more qualitative models, or models that combine qualitative and quantitative techniques, is a relatively recent development.

When underlying mechanistic models are vague or nonexistent, physicians are forced to reason using empiric associations such as those reported in clinical studies. Much of the knowledge of medicine is of this type. Medical AI researchers have accordingly also begun to look at how expert systems might reason using the kinds of data found in the clinical literature.[29] In this work the "models" are those of statistics and clinical trials rather than mechanistic explanations of observed phenomena.

The Logistics of Human-Computer Interaction

As medical artificial intelligence has begun to move from research laboratories into clinical settings, there has been a growing emphasis on logistic and design issues that will en-

*A "mouse" is a mechanical device named for the taillike cord that connects it to the computer terminal. The user rolls it on the adjacent desktop to control the location of a pointer on the display screen. Items of interest are selected by moving the mouse so that the pointer on the screen is positioned over them and then pressing a button on the top of the mouse.

courage physicians to use computers and assure that they are viewed as a helpful tool rather than as a hindrance to efficiency or as a professional threat. For example, there has been an emphasis on giving advice systems an ability to explain their reasoning, a requirement that seeks to clarify and emphasize the physician's role as the ultimate decision maker in patient management.[30] There has also been a large and growing research effort in the area of human-computer interaction, with studies of alternate interactive techniques (such as keyboards, number pads, touch screens, mouse pointing devices, light pens, speech input) and time-motion studies of clinical settings to provide insight into how best to integrate computational tools in routine patient care environments. It is highly likely that advances in such areas will be as important to the clinical impact of decision-support technologies as will be progress in the fundamental research topics mentioned earlier. A related issue is the inherent resistance to using computers that is frequently mentioned by physicians; until this can be overcome through education and experience, it is likely that medicine will remain among the last areas to benefit from the new decision-support technologies that are beginning to have an impact in other areas of science and society.

An Example of an Expert System

ONCOCIN is an advanced expert system for clinical oncology that has been under development at Stanford University School of Medicine since 1979.* It is designed for use after a diagnosis has been reached, focusing instead on assisting with the management of patients with cancer who are receiving chemotherapy. Because anticancer agents tend to be highly toxic and because their tumor-killing effects are routinely accompanied by damage to normal cells, the rules for monitoring and adjusting treatment in response to a given patient's course over time tend to be complex and difficult to memorize. ONCOCIN integrates a temporal record of a patient's ongoing treatment with an underlying knowledge base

*The author is principal investigator for the ONCOCIN project, an effort by physicians and computer scientists under grant support from the National Library of Medicine and the National Institutes of Health's Division of Research Resources. L. Fagan, MD, PhD, is Project Director, and oncology collaborators include C. Jacobs, MD; R. Carlson, MD; B. Sikic, MD, and R. Lenon, MD.

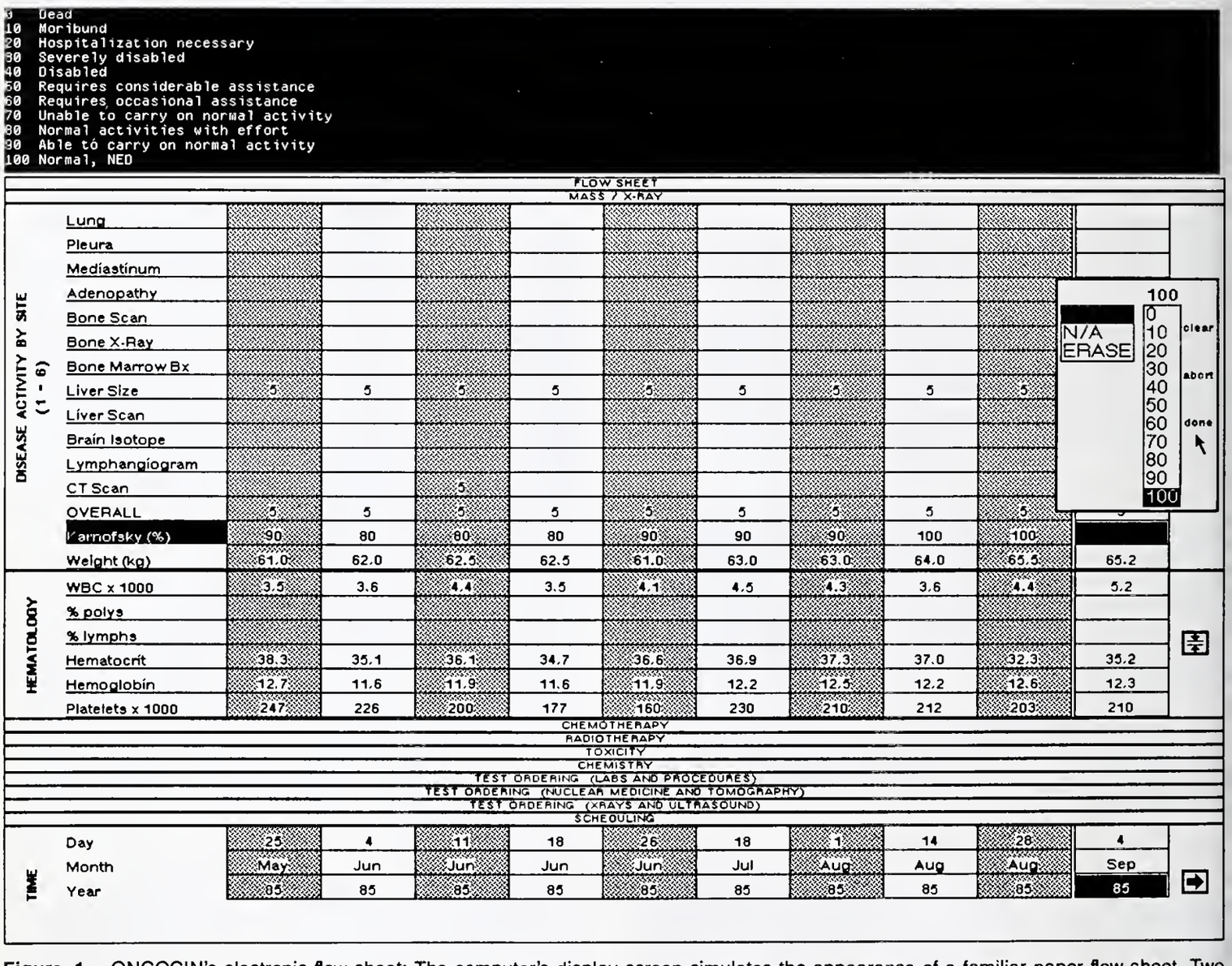

Figure 1.—ONCOCIN's electronic flow sheet: The computer's display screen simulates the appearance of a familiar paper flow sheet. Two sections ("windows") of the form are shown open: "hematology" and "disease activity by site." Closed sections (labeled horizontal bars) may be opened by simply selecting one or more of them with a mouse pointer. In this figure, the physician is logging in the patient's Karnofsky status in the right-hand column of data for the current clinic visit (September 4, 1985). A customized menu register is displayed (see arrow pointer at middle right, controlled by the mouse), and a dark "explanation window" at the top of the screen shows the meaning of the various options for the current data field.

of treatment protocols and rules for adjusting dosage, delaying treatment, aborting cycles, ordering special tests and similar management details. The program uses such knowledge to help physicians with decisions regarding the management of specific patients. This article cannot provide a detailed description of ONCOCIN; other publications have reported the basic system design,[31,32] the results of clinical evaluations[19,33] and the nature of the physicians' interface.[34] Instead, we will briefly describe how this system has addressed the AI research issues outlined in previous sections.

The Logistics of Human-Computer Interaction

A major lesson of past work in clinical computing has been the need to develop methods for integrating a system smoothly into the patient-care environment for which it is intended.[32] In the case of ONCOCIN, the goal has been to provide expert consultative advice as a by-product of the patient data-management process, thereby avoiding the need for physicians to go out of their way to obtain advice. It is intended that oncologists use ONCOCIN routinely for recording and reviewing patient data on the computer's screen, regardless of whether they feel they need decision-making assistance. This process replaces the conventional recording of data on a paper flow sheet and thus seeks to avoid being perceived as an additive task. In accordance with its knowledge of a patient's chemotherapy protocol, ONCOCIN then provides assistance by suggesting appropriate therapy at the time that a day's treatment is to be recorded on the flow sheet. Physicians maintain control of the decision, however, and can override the computer's recommendation if they wish. ONCOCIN also indicates the appropriate interval until a patient's next treatment and reminds the physician of radiologic and laboratory studies required by the treatment protocol.

Although the original ONCOCIN prototype was developed on a large time-shared computer,[19,31] it was clear that disseminating the technology to clinics and private offices would require transferring the system to smaller, less expensive machines. ONCOCIN has thus been rewritten to run on single-user LISP machines, computers optimized to run the LISP programming language mentioned earlier. (We use Xerox 1100 series workstations, but similar LISP machines are available from several other manufacturers.) In addition to large memories and enough power to handle systems the size of ONCOCIN, such machines provide high-quality graphics screens and mouse pointing devices. Thus, ONCOCIN's interface for physicians has been redesigned to take advantage of these advanced graphics capabilities.[34]

The interface (Figure 1) uses multiple movable "windows" to simulate a traditional paper flow sheet used in an oncology clinic.* Each window represents a section of the flowsheet. Because not all the sections can be viewed simultaneously—as they would more than fill the screen—individual windows can be "closed" or compressed when not in use. A physician enters data on ONCOCIN's flow sheet using the mouse pointer and specially developed software input devices called "registers." Such registers are displayed on the screen and manipulated using the mouse and its selection button. For example, registers let the physician select an item from

*The interface system described here has been largely the work of C. Lane and C. Wulfman, MS.

	To determine the dose of methotrexate administered in VAM chemotherapy in protocols 20-83-1 and 2091:
If:	the serum creatinine level (in mg per dl) exceeds 1.5
Then:	do not give methotrexate

Figure 2.—A simple ONCOCIN rule: Rules in ONCOCIN are conditional statements that indicate circumstances under which a given conclusion can be reached about a patient's management. The rule shown is one of many that could simultaneously be applied in considering the case of a patient undergoing protocol-directed therapy for small-cell carcinoma of the lung. VAM = VP-16-213 (etoposide), Adriamycin (doxorubicin) hydrochloride and methotrexate

choices (displayed on a "menu") or enter numbers (using a graphic calculator keypad). Registers have been built for almost every kind of data input on the flow sheet; the computer's keyboard is used to enter only textual information such as names and addresses. Because such text information is generally entered once by a data manager when the patient is first seen in the clinic, registers and the mouse pointer allow physicians to avoid using a keyboard.

Although ONCOCIN at first appears to be designed as a data-management tool for following events that occur over time, there is an underlying reasoning element that uses the data as they are entered, along with a patient's historical information, to determine the recommended therapy for that clinic visit. The knowledge for making such decisions is derived from chemotherapy protocols and from the experience of collaborating oncologists who have assisted in ONCOCIN's development. When the "chemotherapy" section of the graphic form is opened at the end of the session (see Figure 1), recommended drug doses are automatically filled in on the flow sheet by the computer, and the explanation window provides the reasons for any dosage attenuation, delays in treatment or aborted cycles of chemotherapy that have been recommended. The physician may override such advice by simply entering a different drug dose on the flow sheet in lieu of ONCOCIN's suggestion.

Symbolic Representation of Knowledge

The internal knowledge representation for ONCOCIN is based on the notion of decision rules such as those described earlier.* There are hundreds of such rules in ONCOCIN, some of which are specific to particular treatment protocols and others of which apply generally across all cancer management strategies. Many encode management heuristics provided by oncologists and never explicitly stated in protocol documents. A typical simple ONCOCIN rule is shown in Figure 2. Such rules are internally arranged in a data structure that reflects the hierarchic organization of the field of cancer chemotherapy (Figure 3). By storing rules in the computer in accordance with such hierarchic conventions, it can be assured that knowledge is considered and applied only when the context is appropriate. For example, the rule shown in Figure 2 is explicitly associated with the drug methotrexate, chemotherapy VAM (VP-16-213 [etoposide], Adriamycin [doxorubicin] hydrochloride and methotrexate) and protocol 20-83-1 or protocol 2091 (see Figure 3); it would never be considered if methotrexate were being administered in some other situation.

*The knowledge representation scheme used on ONCOCIN has been largely the work of S. Tu, MS; M. Kahn, MD; M. Musen, MD, and J. Ferguson.

Reasoning With Symbolic Knowledge

The reasoning strategy used by ONCOCIN is guided by the hierarchic structure of the knowledge base described earlier. The focus of attention within the hierarchy at any given time determines the reasoning context and thus the rules that are likely to be pertinent. Because a physician may enter information on the flow sheet in whatever order seems most natural for a given case, however, the system's reasoning

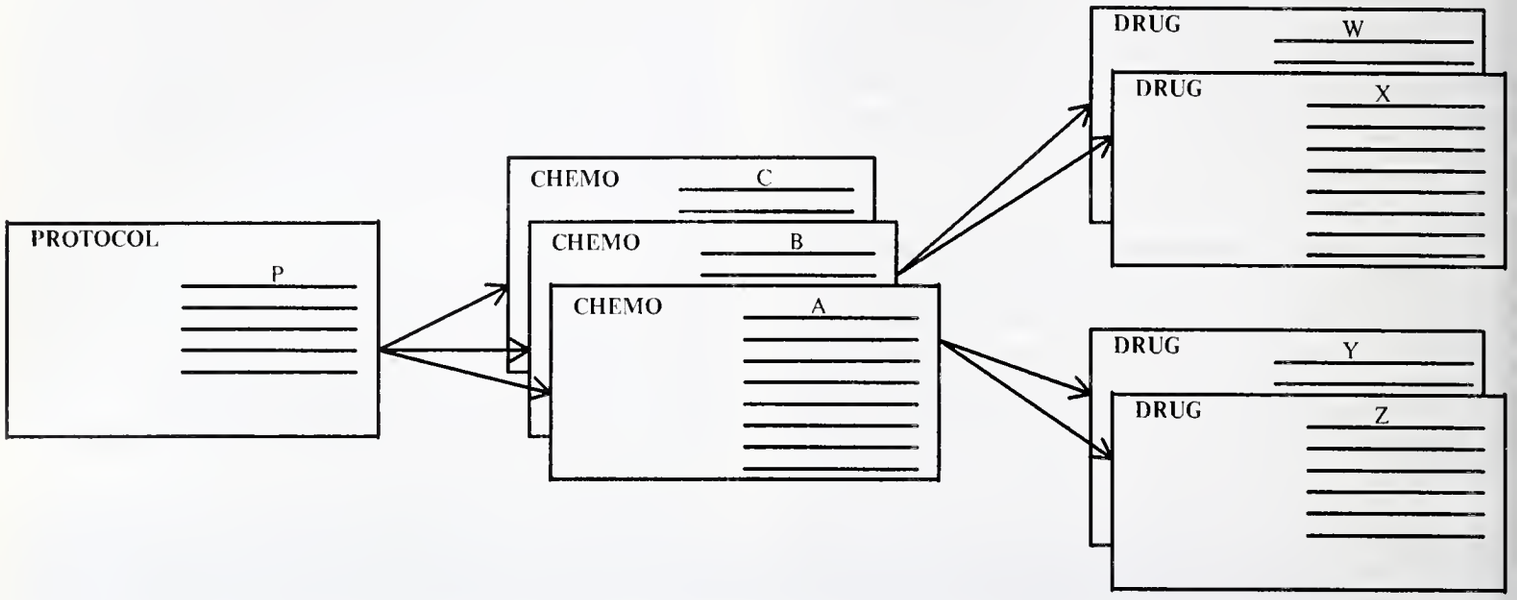

Figure 3.—A portion of ONCOCIN's domain hierarchy: Relevant concepts in ONCOCIN's knowledge base are naturally organized according to the hierarchy shown here. In this example, a protocol *P* involves treatment with chemotherapies *A, B* or *C*. Chemotherapy *A* requires administration of drugs *Y* and *Z*, whereas chemotherapy *B* uses drugs *W* and *X*.

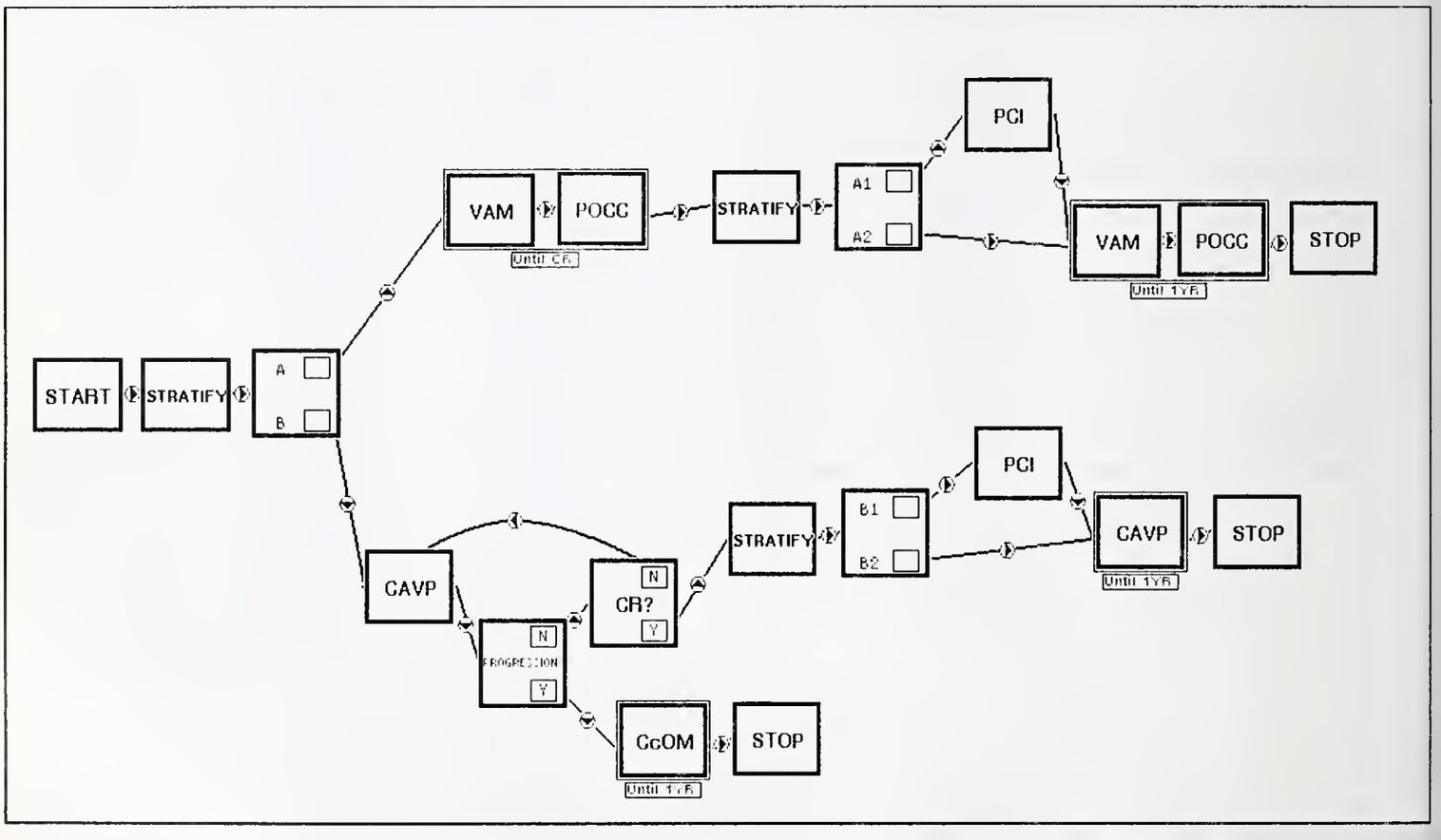

Figure 4.—The schematic description of a protocol entered using OPAL: Flow charts of this sort are entered by manipulating boxes on the display screen and using the mouse pointer to indicate connections between them. The procedural descriptions correspond to flow diagrams included at the beginning of most protocol documents. Individual boxes stand for events such as chemotherapy—for instance, VAM (VP-16-213 [etoposide], Adriamycin [doxorubicin hydrochloride] and methotrexate), POCC (procarbazine hydrochloride, Oncovin [vincristine sulfate], CCNU [lomustine] and cyclophosphamide) or CAVP (cyclophosphamide, Adriamycin and VP-16-213)—or radiation therapy—for instance, prophylactic cranial irradiation (PCI). The diagram shown here represents the schema for a protocol for small-cell carcinoma of the lung in use at our institution. Note that cases are stratified and patients randomly assigned to one of two arms (*A* and *B*) designed to compare different chemotherapies (using VAM and POCC combined versus using CAVP), with subsequent randomization to assess the effect of PCI. CcOM = CCNU, Oncovin and methotrexate; CR = complete remission

strategy must also respond to patient data as they are entered. Schemes have accordingly been devised so that data entered by the physician are remembered but not actually used until they are needed by the hierarchically guided reasoning system. To minimize conflicts between the data the physician chooses to enter and the information needed by the reasoning system, the interactive screen environment suggests pathways through the flow sheet that will result in the most efficient consideration of a given case (ONCOCIN highlights those regions of the screen where it would next like to see data entered). But the ultimate organization of the data-entry process is intentionally left to the physician. Thus, ONCOCIN's reasoning strategy is determined both by the nature of the interaction between a physician and the computer-based flow sheet *and* by the hierarchical organization of its knowledge. It accordingly does not fit cleanly into any single reasoning category but has both data-directed and goal-directed features.

Acquiring and Encoding the Knowledge

Early knowledge-base development for ONCOCIN was arduous and time-consuming. It was difficult for project knowledge engineers to study chemotherapy protocol documents and to encode their contents in accordance with ONCOCIN's knowledge representation scheme. In addition, there were frequent gaps in protocol logic that required extensive sessions with oncology collaborators who helped interpret the several areas in which protocols were ambiguous, incomplete or internally inconsistent. As the structure of the oncology domain became clearer (see, for example, the simple hierarchy in Figure 3 that emerged from the knowledge-engineering process), we developed the notion of a knowledge acquisition system that would permit expert clinicians to enter protocols directly onto ONCOCIN's knowledge base. The resulting system, known as OPAL, has been used experimentally by the collaborating oncologists on the

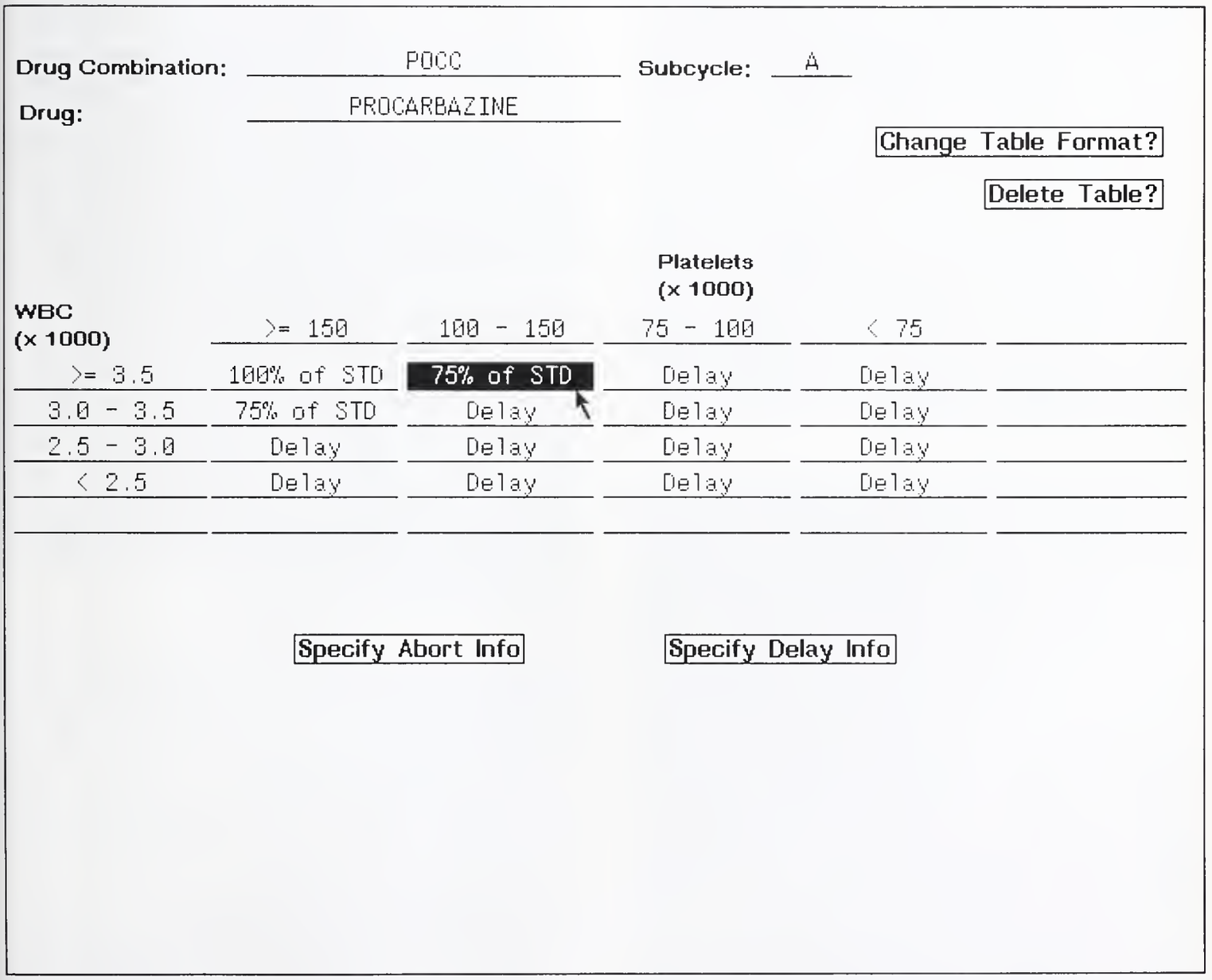

Figure 5.—A sample OPAL form: Much of an interactive session with OPAL requires completing forms such as the one shown here. As in the ONCOCIN interface (Figure 1), most entries may be completed by pointing at areas of interest and selecting from a customized register that appears on the screen. Here an oncologist has entered a dosage-attenuation schedule for procarbazine hydrochloride when it is given in the *A* subcycle of POCC (procarbazine hydrochloride, Oncovin [vincristine sulfate], CCNU [lomustine] and cyclophosphamide) chemotherapy. The highlighted choice indicates that when a patient's leukocyte count (WBC) is greater than or equal to 3,500 per μl and the platelet count is between 100,000 and 150,000 per μl, 75% of the standard dose (STD) should be administered.

project.* Early experience suggests it will greatly facilitate the process of protocol entry and modification for ONCOCIN.

OPAL is a graphical program for use by an oncologist who wishes to enter a new chemotherapy protocol for use by ONCOCIN or to edit an existing protocol.[35] Although the system is designed for use by oncologists who have been trained in its use, it does not require an understanding of the internal representations or reasoning strategies used by ONCOCIN. The system may be used in two interactive modes, depending on the type of knowledge to be entered. The first permits the entry of a graphical description of the overall flow of the therapy process (Figure 4). The oncologist manipulates boxes on the screen that stand for various steps in the protocol. The resulting diagram is then translated by OPAL into computer code for use by ONCOCIN. Thus, by drawing a flow chart that describes the protocol schematically, the physician is effectively programming the computer to carry out the procedure appropriately when ONCOCIN is later used to guide the management of a patient enrolled in that protocol.

OPAL's second interactive mode permits an oncologist to describe the details of the individual events specified in the graphical description. For example, the rules for administering a given chemotherapy will vary greatly depending on a patient's response to earlier doses, intercurrent illnesses and toxicities, hematologic status and so forth. Figure 5 shows one of the forms provided by OPAL for this type of specification. It permits the entry of an attenuation schedule for an agent based on a patient's leukocyte count and platelet count at the time of treatment. Tables such as this are generally found in the written version of chemotherapy protocols. Thus, OPAL permits oncologists to enter information using familiar forms displayed on a computer screen. The contents of such forms are subsequently translated into rules and other knowledge structures for use by ONCOCIN.

Model-Based Reasoning

Although the knowledge of cancer chemotherapy is rich and complex, protocols seldom refer directly to underlying models of drug action. The guidelines in a protocol are, rather, high-level composite descriptions of expert advice, based on the study designers' experience and biologic models of the therapeutic agents and their mechanisms of action. We have observed, however, that when protocols fail to cover a complex clinical situation that arises for a given patient, expert oncologists will turn to underlying mechanistic models and use them to assist in the decision-making process. ONCOCIN has no such knowledge; it must therefore occasionally decline to make a recommendation and instead refers a physician to the study overseer for a decision about how to manage a particular complex problem. It is accordingly a long-range goal to add model-based expert-level reasoning to ONCOCIN's performance.

Our research in oncologic model-based reasoning is embodied in a program known as ONYX.† This system is based on the observation that creative planning strategies in the oncology domain (and many other fields) appear to involve a three-step process[36]: (1) heuristically generating a small number of plans, that is, plausible responses to the problem at hand, (2) mentally simulating (also called "envisioning") how a patient would respond over time if each of those plans were carried out and (3) selecting a preferred plan based on the likelihood of the various possible outcomes and the value placed on those outcomes by the patient and physician. Step 2 in this process involves patient-specific simulation of tumor pathophysiology and drug action but it also depends on recognizing that the outcomes of interventions cannot be predicted with certainty and that probabilistic predictions are more realistic. Thus, model-based probabilistic simulations in ONYX are coupled to a decision analytic module that assists with the third step in the process. Although the work outlined here is preliminary, the proposed planning architecture appears to be a fruitful area for basic research in medical artificial intelligence.

*OPAL is largely the work of D. Combs, M. Musen, MD, and J. Walton.

†ONYX is largely the work of C. Langlotz, MS; H. Rappaport, MD; S. Tu, MS; M. Kahn, MD, and R. Bhatia.

Conclusion

As the ONCOCIN project shows, applied work in medical expert systems typically touches on a broad range of research issues ranging from logistic (such as system integration) to psychological (such as designing human-computer interfaces) to theoretic (such as causal model-based reasoning). It is this melding of real-world needs with promising technologies and challenging theoretic concerns that has made the field of medical artificial intelligence particularly appealing to the physicians and computer scientists working in the area. The long-term challenges are well recognized—such as the need for mechanisms that will assure completeness and currency of shared knowledge bases, or the need for integrated computing systems that will allow physicians to access a variety of expert systems and other computational tools from a single workstation in their office or on the hospital wards. Yet, it is only through enhanced educational opportunities for health personnel that we will see the emergence of physicians who can identify the quality systems from among those that are available and accept the computer's role as a knowledge-enhancing tool rather than as a replacement for a physician's own thoughtful assessments. It is ultimately an informed professional community that will determine the clinical impact of medical advice systems.

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Laboratory Medicine in the Age of Information

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Information systems in laboratory medicine reflect and respond to the major changes now taking place in health care. This fruitful and practical area for medical information science encompasses problems in medical information science, shop floor control and issues in clinical behavior.

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Computers . . . have penetrated our daily lives and are becoming society's central nervous system.

TOHRU MOTO-OKA, PROFESSOR, TOKYO UNIVERSITY
The Fifth Generation Computer Project[1]

Today, in the new, aggressive, health care marketplace, hospitals vie openly with their peers for attention, for patients and for physician allegiance. Faced with a decline in reimbursement for inpatient care and a reduced demand for general inpatient facilities, hospitals are diversifying and specializing their services.[2] New outpatient programs emphasize preventive medicine and wellness. Surgicenters and clinics have been opened that use the technology of their full-service support departments without incurring the cost of inpatient overhead. Some inpatient facilities have been redesignated as "critical care centers," organized around the advanced diagnosis and management of specific medical problems. (To solidify referrals from primary care facilities, patients seen at such centers are often then returned to their referring community hospital and to their physician for follow-up care.) All of these activities seek to extend the influence and the catchment areas of full-service institutions by establishing outreach networks of collaboration.[3] Invariably, collaboration—and the marketing of collaboration—depends on information.

In every hospital's search for competitive advantage, clinical laboratory tests represent a particularly favorable information product because they are carried out at a physician's request, are done on many specific patients, are individually inexpensive (as medical services go) and only a specimen need be transported. Thus the delivery of responsive, differentiated and reliable laboratory services, identified with the logo of the hospital, can become a natural extension of that hospital's marketing strategy.

Laboratory Information

Except for the blood bank, information is the sole medical product of a clinical laboratory. In the past, laboratory reports have generally presented the facts to a predefined audience in a few specific formats. Today's electronic technologies so broaden the communication and reporting options that a laboratory may now act as a clinical decision support service, able to respond to a wide range of demands for clinical decision making.[4] Because the need for new professional revenue is now combined with increased priorities for cost containment and hospital outreach, sufficient incentives exist to bring about this major change in the role of the laboratory. This situation in turn creates a demand for a new generation of robust and flexible laboratory computer systems that can coordinate and distribute the information.

Changing Roles

Fixed price reimbursement for hospital care has undermined the once comfortable position of inpatient laboratories as revenue-generating hospital departments. Now cost centers, they must earn their way by other means. Issues such as overhead, tax and the economies of shared personnel and shared equipment have led laboratories to move out of large hospitals and to form "cluster laboratories" in an effort to provide services among collaborating institutions at a lower cost.[5] Phlebotomy teams and rapid-response laboratories have been left behind at hospitals to collect and organize specimens and to carry out tests that require a rapid turnaround. In addition, these new facilities are acquiring or merging with local reference laboratories that have been serving both physicians' offices and other hospitals that are too small to support their own complete laboratory facilities. Such mergers bring with them not only new clients with different information requirements, but also courier routes, blood specimen-drawing stations and community "stat" laboratories. The result is a set of distributed workplaces that must be rearranged in a coordinated network to offer a broad mix of services characterized by optimal responsiveness at minimal expense. The ability to put together these new laboratory configurations is a striking example of how modern informa-

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tion technologies help a medical specialty to extend and alter its role in response to outside forces. But the difficulties that information systems encounter in doing so point up some limitations in the present laboratory computer logic.

The Information Tools of Laboratory Medicine

Managing a modern clinical laboratory of any size without a computer system is a difficult and labor-intensive task at best. Over the past 15 years effective on-line systems have been widely implemented that have managed to surmount the daunting procedural variety of laboratory subspecialties such as chemistry, hematology and microbiology.[6] Such systems have two basic components: one organizes the work done on the "shop floor" (processing specimens, making test measurements and assembling data for reports), and the other accepts orders and manages the business (posting charges, submitting bills, accepting payments and managing accounts receivable). Both components encompass intricate clerical detail and replace extensive manual clerical tasks.

Until recently, vendor designs have treated laboratories as two separate work environments, each requiring its own kind of system: the hospital laboratory, set up to serve inpatient requirements on a 24-hour basis in a flexible and responsive way, and the reference laboratory, organized to accommodate a large volume of specimens from a diverse patient population, where tests are processed in defined batches with a set time for delivering the results.[7]

From a systems standpoint, the main differences between these two laboratory types rest in how tests are ordered and specimens are brought into the facility, how reports are formatted and delivered, how priority (stat [immediately] and "ASAP" [as soon as possible]) specimens can be introduced into the work sequence and who (patient, physician, hospital or insurance payor) receives the bill. Specific programming solutions to each of these issues have generally been written for each environment separately.[8-10] We will return to these issues, and discuss them from several perspectives.

Difficulties and New Requirements

The distributed type of computer system needed to serve both the hospital (or many hospitals) and the community is implicit in the networked work-station orientation of present laboratory system designs. Today's systems already maintain overall supervision across many sites by means of computerized record keeping and electronic communication. When reference work and hospital work have been merged, however, present-generation software faces serious practical problems:

- New requirements for accepting specimens meet with frustrating rigidities of computerized procedures.
- Printing and managing new kinds of reports turn out to be perplexingly awkward.
- Billing a client base by different rules runs into unexpected specificities of design.

These problems appear so straightforward that it is surprising to find that the necessary logical modifications and enhancements needed to overcome them are unexpectedly difficult to carry out. Moreover, these difficulties must be resolved before the next and more interesting steps in combined automation can be carried out.

Ad Hoc Change

No laboratory system will be used unless it can guarantee the completeness and consistency of operations in its very complex procedural environment.[11,12] A computer must assure that all orders are recorded, all specimens are accounted for, all measurements made, all data are in agreement with controls and all reports are complete and correct. If errors appear even occasionally, penalizingly expensive human controls must be introduced.

The requirement for completeness and consistency is further complicated, first, by allowing expedited orders to be merged with regular orders, and, second, by allowing orders to be modified, as it were, in midstream. For instance, even after an order has been given, a specimen received and after measurements are under way, the process may be interrupted by a change in orders from a physician: add-ons, partial cancellations or a step-up in priority. Because these changes in orders usually represent an increased interest and attention on the part of a physician with respect to a particular patient, how well a system can respond to such changes is a major measure of its effectiveness. This sensitivity is further enhanced if the reputation of a hospital for reliable, responsive service is on the line.

To meet such extraordinary service requirements, every laboratory order must be handled as if it could become an exception—although the incidence is small—and all such exceptions, when they occur, must be manageable within the checks and controls provided by the system.[13]

This approach contrasts with the industrial shop floor, where the basis for control is to handle exceptions separately and even with a delay. Only a few systems outside of medicine, such as airline reservations systems, attempt to cope with the ever-present potential for rescheduling. (Flights and charges, for example, can be changed in the middle of a trip, but often with considerable interaction at the terminal.)

Hard Coded Controls

The weave of control mechanisms built into the logic of laboratory systems appears to be the major stumbling block to introducing new tasks or new ways to carry out established tasks in today's software. To cope with certain kinds of ad hoc change without loss of reliability, control tables and cross checks have been introduced in ways that are so integral to the specific design that they defeat the simplest modifications and enhancements. Although freed from the concept of in-line coding, most medical systems have not been freed from hard coded controls.

One systematic approach to this problem—but not a very general one—is to keep a temporary file on the internal transactions of every open order that not only traces what has been done, but also documents the index of every table and file change that the order and its processing introduces.* The retained audit trail is sufficient, using a little algorithmic intelligence, that changes can be made and entries reversed selectively on demand. Appropriately implemented, this becomes a tool that sufficiently uncouples operations from controls so that individual subroutines representing new functions can be added without revising the entire control structure.

*This system solution was designed by Philip Blume, MD, for the clinical laboratory of The Hospital of the Good Samaritan, Portland.

Post Accessioning

An example of a capability generally missing in hospital-based laboratory systems that is a practical necessity in a reference laboratory environment is the capability to carry out what might be called "post accessioning"—that is, the capacity to start a specimen through the laboratory and place the order in the computer after the fact. This violates an obvious sequence required for laboratory control by splitting the clerical task of recording orders away from the initial processing of the specimen so that they can proceed concurrently. The approach has been introduced so that deadlines can be met when outpatient specimens are delivered in such volume that a serious delay would result from sequential work. The technique uses special temporary control numbers (gummed labels that link a specimen with its order) that are subsequently linked to the regular patient identifiers and control indices as soon as order entry is complete. For anyone familiar with such prosaic procedures, the potential for error and a self-defeating proliferation of manual clerical controls is obvious. An insistence on check digits as a regular part of the system and the use of the audit utility outlined above make it a simple matter to add this feature when the need arises. Similar enhancements are designed for reporting and billing procedures. Once these system incompatibilities are resolved, it is possible to shift the laboratory focus from providing test results to marketing a decision support service.

Markets for Information

The analysis needed to provide different kinds of clinicians in different work settings with reports that meet their specific concerns is a part of medical informatics. At the same time, the heuristics of medical practice will also sort out the usefulness of possible formats. A number of markets can be tentatively identified.

- There is a market for "numbers"—raw data to be interpreted by clinicians who receive them. This is the information product sought by those whose major focus is cognitive practice—internists, family practitioners, pediatricians and obstetricians (prenatal care).
- There is a market for diagnostic screening panels. Service to outpatients adds incentives for completing a logical sequence of testing on a single specimen. Not only can testing logistics be simplified and testing costs reduced, but patient-related clinical judgments can provide for a professional fee. Examples are hepatitis, thyroid and rheumatoid screens. In some cases a test sequence can be devised that chooses among alternative tests as results are determined (reflex testing), or the same sequence can be run in software on the results of a panel, if it proves less expensive to do the run all at once.
- There is a market for data in context—diagnostic interpretations or priorities for the convenience of those practitioners who look upon the laboratory as a team collaborator. This might include general surgeons, gynecologists and orthopedists in smaller hospital facilities where a surgical pathology department already establishes a lively diagnostic interchange with the same staff. Today, in larger institutions, "intensivists"—hospital-based internists—are more likely to take this role.
- There is a market for esoteric tests and their interpretation. Here the methods and the numerical results may be so intricately intertwined that the measurements alone can be insufficient. Often laboratory cross reactions are related to the specific method chosen, and in some instances—such as tests for the human immunodeficiency virus (formerly HTLV-III)—the results are charged with soeial implications.
- There is a market for special surveillance—indeed, it is expected that critical values and other significant results where time is important will always be brought to the attention of the clinician. At the same time, it is important to keep unnecessary "urgent" reporting to a minimum.
- There is a market for special services—the changes in orders noted above, where additional tests are added to a specimen already in hand or tests are cancelled or partially cancelled without charge.
- There is a market for trended data in situations such as chemotherapy where laboratory changes over time are a guide to present action. In integrated patient care systems, the timing of laboratory results with medication and with clinical events strengthens the decision-making context.

Each of these situations sets up its own information requirement for hard copy reports, for direct advice and also for interactive computer dialogue.

The shift in organizing laboratory services presages similar changes in health care generally. Information and information systems are now becoming key coordinative tools that link the health care activities of a full-service medical center to the community. Today more than 75% of hospitals with more than 300 beds offer home health care. More than 60% inelude medical office buildings on their campus and most are opening centers and elinics for a wide variety of outpatient services. More than 60% offer wellness programs.[14] Laboratory information is but one thread that leads from the bedside to the office and from the clinic into the home. Those institutions that can integrate information in the service of patient care to a greater advantage than their competitors will be in the best position to provide quality services at a reasonable price in the 1990s and beyond.

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The Case for Using Computers in the Operating Room

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The largest cost center and revenue generator in most hospitals, the operating room is subject to demands for increased cost accountability and quality assurance. Information technology tools can be incorporated into the operating room and have the potential to positively affect practices there through addressing nursing, administrative/financial and medical needs. Microcomputer-based operating room systems now on the market can provide functions from scheduling and case costing to medical records and market analysis. Of 21 functions identified, 10 can be characterized as mandatory and the remaining as optional. Individual systems offer varied configurations, providing from 0 to 21 functions. These enhanced capabilities for data collection, monitoring and analysis enable health care professionals to provide both better and more cost-effective care for surgical patients.

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Over the past 20 years, the computer has had a major impact on hospital information resources management. A historic perspective makes evident two areas where computerization has made its earliest and greatest contribution.[1] The first area includes activities that require a high volume of repetitive data processing. The other area encompasses the services in the health care environment that generate high levels of revenue.

Thus, the computer found a home first in the business office and from there moved on to the clinical laboratory, then to the pharmacy and radiology departments. During the past decade, computerization has been implemented in practically all other areas of the hospital such as central supply, dietary services and medical records.

Remarkably, however, one of the areas that fits both criteria for early introduction of computerization has only in the past few years emerged as a major locus for computer use. This is the hospital surgical suite. Unlike the laboratory, where a high level of transactions occurs with a single laboratory test, in the operating room a high volume of information is obtained with a relatively low level of transactions. This attribute characterizes the surgery environment and presents a special set of concerns when computerization is discussed.

In this paper we intend to examine the needs of the surgical suite, to describe the capabilities of computing to meet those needs through a detailed review of available software packages and to discuss the potential effect of computerization on operating room practices.

Needs of the Operating Room

Today the operating room (OR) serves as a theater for the more radical and innovative medical practices. It is also the main source of hospital admissions in this time of decreasing inpatient days. The largest cost center in the typical hospital, it is one of the last areas to become subject to cost accounting. Thus, the long-standing problems of scheduling operating room use are compounded by administrative concerns regarding cost efficiency and documentation as operating rooms are subject to intensifying scrutiny, especially in the areas of quality assurance and cost containment.

For hospitals now facing the cost-accountability requirements of diagnosis-related groups (DRGs), this constitutes a major problem. According to a recent study, most hospitals surveyed report increased activities to analyze surgical costs in response to DRGs.[2] A cost center as well as a revenue center, the OR must provide ongoing statistical records to account for the cost effectiveness of material, fiscal and human resources.[3]

To address cost-containment issues and the related area of quality of care, hospitals clearly need improved management and utilization tools. "This challenge is also an opportunity to rethink the basic principles of OR management, to explore

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ABBREVIATIONS USED IN TEXT

DRG = diagnosis-related group
JCAH = Joint Commission on Accreditation of Hospitals
OR = operating room

new ways of reducing costs, and to develop new relationships and more efficient management procedures."[4] To do so, health care professionals must first collect reliable data and then complete an objective diagnosis.

In the recent past, the attempt to address scheduling difficulties very often resulted in the creation of additional operating rooms, requiring the allocation of more resources to these costly facilities. With the advent of DRGs has come tighter management of health care costs, even in the operating room, one of the last areas to be subject to cost constraints. An alternative approach now becoming prevalent involves the systematic review of the surgery arena.

Such review encompasses a wide range of data, for patient care in that arena involves a high volume of clerical work, generally completed by specially designated OR nurses. Among their duties are the following:

- Creating the OR record
- Doing inventory functions
- Recording the details on which billing is based
- Completing clerical housekeeping tasks of varying degrees.

In addition, the nursing staff is responsible for supervising OR activities on behalf of the hospital and ensuring compliance with the guidelines set forth by the Joint Commission on Accreditation of Hospitals (JCAH).

Currently, both data and objectivity are in short supply. It is crucial that professionals take a fresh look at what in fact goes on in operating rooms and how those facilities are managed. This requires analysis, determining use, assessing the current manual systems being used and further assessing the users, both professional health care providers and patients. It also requires defining a set of goals to be addressed in looking at operating room management.

Computerization of the Operating Room

Health care institutions have at this moment the opportunity to utilize the tool of the 20th and 21st centuries, the computer, to harness the data being produced in exponential fashion and to manage those data to generate information that will ultimately result in better care for patients and more effective support for the institutions. To realize this opportunity, health care professionals must address the questions of what information is needed and how it should be applied to the practice of medicine. This necessitates a change from the old data-processing mentality to an information resources management approach. The magnitude of this change is made possible by the new information technologies, but its true potential lies in the capabilities it provides to the health care field.

The task is not simply to obtain access to such tools and bring them into the operating room. "Microcomputers are now a reality in the OR and are already having 'a significant impact on surgical practice'" (Fourth Annual Joint American College of Surgeons/Association of Operating Room Nurses Symposium: "The OR Environment Revisited," *Surgical Practice News*, 1986 Mar, pp 1,7-8). The challenge is to incorporate the tools of information technology into practices that will have a positive effect on the operating room environment and hence on patient care.

Responses to Demonstrated Needs

Three categories or areas of demonstrated need for introducing computer systems in the operating room can be identified: nursing, administrative/financial and medical. All three must be addressed to produce a workable product.

Nursing is the key component that hospitals depend on to deliver their services to patients. Operating room nurses perform a wide range of clerical and clinical functions. With the assistance of information technology, nursing can focus on issues directly affecting the quality of care, including the full range of management concerns in the operating room arena.

Recently developed operating room computer systems offer the capability to support the clerical and managerial functions of the nursing role and also provide needed reports on a specified periodic or a demand basis. In more sophisticated environments, these data can be transported from the operating room computer system to the hospital information system to be integrated into a patient's medical record.

Administrative and financial management concerns must be addressed comprehensively by the new surgical software, as hospitals attempt to cope with the reimbursement revolution resulting from implementing DRGs. As the health care shifts from a cost-reimbursement to a fixed prospective-payment base, it is critical to identify specifically whieh costs occur and where they arise in the treatment of patients. Operating room software provides the capability not only to track these costs, but also to itemize operational expenses in such categories as direct versus indirect and chargeable versus nonchargeable costs.

Medical care issues are also affected by the computer in the operating room. The cost-containment crisis comes at a time of unprecedented focus on the quality of medical care. As medical technology develops, techniques once considered miracles, such as heart, kidney and other organ transplants, have become routine procedures. These and other biomedical advances are accompanied by new legal and financial barriers to providing patient care. The malpractice crisis is accompanied by increased stress on quality assurance.

The environment thus demands that professionals complete cost-benefit analyses of medical treatments, especially in such areas as surgical interventions, where both costs and medical risks are high. Surgeons must have the ability to objectively evaluate and manage each surgical procedure in such a manner as to control the costs associated with nosocomial infections and iatrogenic problems such as surgical accidents and conditions that may manifest themselves postoperatively.

In responding to quality assurance issues and to cost-containment requirements, hospitals have at their disposal the new management tools that information technology provides. These include software packages that support

- Productivity
- Independent learning
- Statistical analysis
- Data base development
- Report functions
- Medical and management decision making.

Other tools enhance clinical activities and communications capabilities. The potential of these tools is just now presenting itself in the form of software packages specifically produced for the surgical suite.

To meet the needs for quality assurance and cost-accounting functions, certain other software features may be required. Selection of a system should be based on a user's specific situation. Features of concern to end users are those that they themselves can evaluate, not those that are of concern only to a computer professional.

Changing circumstances may dictate that any number of items be addressed in varying combinations. Items of interest within the ad hoc reporting function might include

- Instruments and equipment used by a physician, the type of operation, specialty request and repair, statistics and costs.
- Inventory tracking by room, patient, surgeon, results, staff and case type.
- Reports and records statistics by room, staff, case, surgeon, type of operation, diagnosis and outcome.

Software Review

As a research evaluation study of operating room systems indicates, software capabilities can go beyond scheduling to fulfill hospital needs for cost tracking, clinical abstracting and other information requirements in support of the overall goals of cost containment and quality assurance. As part of the study, we reviewed the literature to determine which functions should be considered in evaluating an operating room system.

In all, 21 functions were identified in the literature. Ten were considered important by most of the authors reviewed and therefore are labeled mandatory within this review; 11 were of lesser importance. It should be realized, however, that these lists can serve only as a guide to a specific institution establishing its own set of mandatory and optional functions.

The authors of the evaluation study also analyzed information provided by the vendors of 18 software packages now available, to determine which functions those packages provide.

The mandatory functions include the following:

Scheduling	Staff records
Resource use	Inventory control
Surgeon preference case cards	Case cart supply lists
OR logs	Infection control
Anesthesia	Case costing

The 18 software packages now available were further analyzed to determine which of these functions each package provided. Five of the systems address fewer than five mandatory functions, with one package including no mandatory functions. Three—Enterprise Systems, Intellimed and Health Care Computer Works—offer all ten mandatory functions; six offer nine of the ten. The functions offered most frequently include OR scheduling, anesthesia and OR log recording. Least frequently offered functions are infection control and staff record maintenance. Noteworthy is the fact that the mandatory functions do not include patient-related areas, but rather are limited to monitoring and record keeping in areas prescribed by the JCAH guidelines, standard operating room procedures and hospital accounting requirements. For detailed results, see Table 1.

The additional functions, ranked by the authors reviewed as of lesser importance, include the following 11 areas:

Equipment control	Clinical data
Patient care plans	Patient assessment
Recovery room	Market analysis
Pharmacy	Medical records
Electronic mail	Vendor analysis

Implant information

These functions are provided less frequently than the mandatory functions. In all, 16 of the packages include equipment control and 15 allow for medical records, but other features

TABLE 1.—*Available Computer Mandatory Functions for Operating Rooms**

Vendor	*OR Sched*	*Staff Rcrds*	*Rsrce Use*	*Invnt Control*	*Case Card*	*Infect Control*	*OR Logs*	*Case Cart*	*Anesthesia*	*Case Cost*
Enterprise Systems	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Intellimed	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
De Royal	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Health Care Computer Works	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
CHIRPS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Serving Software	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Atwork	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hospital Software Systems	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Medinvent	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Medical Software Systems	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Micro Med Technologies, Inc.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
First Coast Systems	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
MDAX	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Acme Visible Records	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pro Comp Services, Inc	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Professional Resources Organization	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Hospital Systems	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Association of Operating Room Nurses	No	No	No	No	No	No	No	No	No	No

Case card=surgeon preference case cards, Case cart=case cart supply list preparation, Case cost=case costing/patient billing, Infect=infection, Invnt control=inventory control/management, OR logs=operating room log recording, Rsrce use=resource utilization recording, Staff rcrds=staff record maintenance

*From A. Warnock-Matheron,RN, and K.J. Hannah, RN, "Comparative Analysis of Operating Room Systems: An Evaluation Research Study" (unpublished manuscript).

TABLE 2.—*Additional Available Functions of Computerized Operating Room Systems**

Vendor	Ptnt Asmnt	Recov Room	Mrkt Anal	Equip Control	Pharmacy	Care Plan	Med Rcrds	Elec Mail	Vndr Anal	Clinical Data	Implant Info
Enterprise Systems	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Intellimed	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
De Royal	No	No	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes
Health Care Computer Works	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
CHIRPS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Serving Software	No	Yes	No	Yes	No	No	Yes	No	No	Yes	No
Atwork	Yes	No	Yes	Yes	No	No	Yes	No	Yes	No	Yes
Hospital Software Systems	No	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Medinvent	No	Yes	No	Yes	Yes	No	Yes	No	No	No	Yes
Medical Software Systems	No	No	No	Yes	No	No	No	Yes	No	No	No
Micro Med Technologies, Inc.	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes
First Coast Systems	No	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes
MDAX	No	No	Yes	Yes	No	No	Yes	No	Yes	No	Yes
Acme Visible Records	Yes	No	No	Yes	No	No	Yes	Yes	No	No	No
Pro Comp Services, Inc	No	No	Yes	No	No	No	Yes	No	No	No	Yes
Professional Resources Organization	No	No	Yes	Yes	No	No	No	No	No	No	Yes
Hospital Systems	No	Yes	Yes	Yes	No	No	Yes	No	No	No	Yes
Association of Operating Room Nurses	No	No	No	No	No	No	No	No	No	No	No

Care Plan=patient care plans, Elec=electronic, Equip=equipment, Info=information, Med Rcrds=medical records, Mrkt Anal=market analysis, Ptnt Asmnt=patient assessment, Recov=recovery, Vndr Anal=vendor analysis

*From A. Warnock-Matheron, RN, and K.J. Hannah, RN, "Comparative Analysis of Operating Room Systems: An Evaluation Research Study" (unpublished manuscript).

are less frequently provided. Only three systems provide care plans. Table 2 details the results.

Two packages, CHIRPS and Intellimed, offer all 21 functions. Three, Enterprise, Health Care Computer Works and Micro Med Technologies, offer 18 functions. For a complete ranking, see Table 3.

Vendors of all 18 software packages reviewed indicated that they had the ability to support the production of user-defined reports; thus, the presence or absence of specific reports or online inquiries is not at issue. Needs, however, cannot be met effectively without the provision of a report generator or a high-level query language that allows users to produce ad hoc reports without vendor or inhouse programming support.

TABLE 3.—*Ranking of Computer Systems by Functions**

Vendor	Total Functions	Mandatory Functions
CHIRPS	21	10
Intellimed	21	10
Enterprise Systems	18	10
Health Care Computer Works	18	9
Micro Med Technologies	18	10
Atwork	16	10
Hospital Software Systems	16	10
De Royal	15	9
Hospital Systems	14	9
Medinvent	14	9
Acme Visible Records	13	9
Serving Software	13	9
MDAX	13	8
First Coast Systems	13	7
Medical Software Systems	11	9
Pro Comp Services	11	8
Professional Resources Organization	11	8
Association of Operating Room Nurses	0	0

*From A. Warnock-Matheron, RN, and K.J. Hannah, RN, "Comparative Analysis of Operating Room Systems: An Evaluation Research Study" (unpublished manuscript).

Certain caveats should be noted by those considering acquiring this software. First, the packages reviewed should be considered at this point as stand-alone systems. Extensive data definition and data-base development would be required before linkages between systems become possible. "Even the common notions like admission, discharge, bed-day, ward, etc, often turn out to lead to confusion" (Fourth Annual Joint ACS/AORN Symposium: "The OR Environment Revisited," *Surgical Practice News,* 1986 Mar, pp 1,7). Second, response time and other technical aspects can be objectively measured only through a formal benchmarking process. Third, cost comparisons must be weighted by performance considerations.

Potential Effect of Computerization

The software packages available make it possible for health care professionals to gain control of data produced in areas as diverse as infection control, case cart supplies and surgeon preference case cards. The resulting information can serve not only to establish enhanced knowledge bases but also to change the operating room environment. Computerization makes possible improved care for surgical patients through analysis in the areas of:

- Operating room practices and techniques,
- Efficiency and productivity factors,
- Treatment outcomes, alternatives and objectives,
- Scheduling, staffing patterns and performance,
- Costs incurred in specific procedures.

Thus, computerizing the operating room functions can enable health care institutions to allocate resources and manage assets and costs more effectively. By relating costs not only to financial return but also to procedures, techniques and medical risks, medical practitioners will meet more capably their responsibility to patients—a responsibility nowhere more evident than in the surgical suite.

The recently revised JCAH standards on quality assurance

require that hospital surgical staffs establish mechanisms to monitor and evaluate patient care. A monthly review of all cases is recommended. The effect of these revisions is to move the concept of monitoring beyond "random identification of problems to systematic, facility-wide screening."[5] The considerable demands that these revisions place on the operating room environment may in fact be amplified as the JCAH completes its new chapter on surgical quality standards to be included in its accreditation manual.

Fortunately, in this time of unprecedented pressures to control costs and risks, software packages such as those reviewed above are now available for the operating room arena. Designed to run on machines with increased speed and enlarged memories, such as the IBM AT-RT and the A T & T Company's 3B type microcomputers, these packages mark the beginning of the development of sophisticated fourth-generation data bases and associated applications software, producing systems to be used by medical and management professionals as well as support personnel.

Thus, within information technology exists the capability to address the spectrum of needs in the operating room, facilitating the delivery of cost-effective, high-quality medical care. The computer may be late in entering the surgical suite, but it brings with it invaluable tools for managing that complex environment.

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Radiology Systems of the 1990s—Meeting the Challenge of Change

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Digital imaging technology, particularly reconstructed images such as computed tomography and magnetic resonance imaging, has fueled the increased demand for radiologic services but has intensified storage and communications problems. Today more than 25% of radiologic examinations are digital in origin and, with progressive replacing of film images by digital images likely through the introduction of imaging plate technology, the radiology profession is undertaking the massive effort of evolving a new system where digital images will be transmitted, stored, retrieved and displayed by a multicomponent system connected by a local area network. Through this system, images will be nearly instantly accessible to anyone who needs them.

A leading hypothesis is that when the volume of digital examinations reaches 50% of the whole, cost and efficiency considerations will lead to a massive conversion to the digital image management system, which will progress spontaneously. This conversion, unless planned for in today's equipment acquisitions, could lead to great economic stress in hospitals. The 50% point may be reached by the early 1990s.

(Lodwick GS: Radiology systems of the 1990s—Meeting the challenge of change, *In* Medical informatics [Special Issue]. West J Med 1986 Dec; 145:848-852)

In the past 30 years, the field of radiology has changed from a narrow discipline located in the basement of hospitals to a dynamic set of interrelated specialties functioning at the heart of medical practice. This change is related to the broadening of the scientific base of radiology. Foremost has been the revolutionary improvement in image quality and the speed with which image information can be captured. New contrast agents and selective catheterization have allowed the dynamic imaging of vascular organs; new nuclear tracers provide highly sensitive imaging technologies for detecting disease. Radiologists now take biopsies of tumors and drain abscesses. A truly fundamental advance is the computed reconstruction of images, which has brought digital imaging into the clinical environment. Radiology is now more than a medical discipline; it includes physicists, engineers, computer scientists, radiobiologists and physicians who are the best that our medical schools have to offer. And given the organizational and interdisciplinary complexity of the modern radiologic sciences department, computer-based communications systems are vital to effective functioning.

With the introduction of computed tomography (CT), there is a trend to replace the existing film imaging with digital images. This trend is accelerating to the point where 25% or more of the daily production is digital.[1] While most such digital images are of relatively low information density—512 by 512 pixels by 8 bits or less—a new imaging technology that uses a solid-state plate and laser scanning for providing high-resolution digital images promises to sharply increase the volume of digital image production. Using this technology, it becomes possible to produce images of high informational content, such as of chest and bone, on high-resolution 2,048 by 2,048 pixel monochrome displays ("Manipulating Digital X-rays Enhances Different Features," *Electronics*, Feb 3, 1986, pp 39-41). Given the volume of image production in a busy department, if all images were digital, the amount of new digital information that would need to be stored, transmitted and displayed is more than 4 gigabytes per inpatient bed per year.[2] In fact, each patient's images need to be displayed as many as ten times during the first week of hospital admission.[3] Realistically, we are only beginning to understand the requirements for the systems that comprise a picture archiving and communication system (PACS), and, for this reason, we are not yet ready to implement a radiology information system that can handle this volume.

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ABBREVIATIONS USED IN TEXT

ACR = American College of Radiology
CT = computed tomography
MARS = Missouri Automated Radiology System
NEMA = National Electrical Manufacturers Association
PACS = picture archiving and communication system
RIS = radiology information system

With the volume and proportion of digital images growing steadily without an adequate system for digital image management (PACS) , the pressure is on to identify all of the problem areas and to resolve the issues that surround digital image management. In the meantime, the profession is obliged to compromise by recording digital images on film. Managing film images has long been a thorny problem because all who care for a patient both want and need to see the images at the same time. In a department with poor control of the film library, this demand creates a chaotic situation in which film images are lost or stolen, followed by a sequence of events that tends to delay and, at worst, cripples the process of taking care of a patient.[4] If we could but reverse this trend to provide digital storage and display of all images, then it would be technologically possible for all physicians to see the same images at the same time, and the single most difficult problem in radiology would be resolved.

The Radiology Information Management System

The problem of the film library is not a new one; it just has become less manageable with increased volume and demand. By 1966, with a growing accessibility of computers, new systems for implementing solutions to scheduling, filing, reporting and billing began to appear.[5-10] At first, each system seemed to provide its own unique approach to resolving the radiology management problem; some were oriented to methods of getting a consultation reported in a timely fashion, others to getting the bills out. With the passage of time, it became apparent that certain solutions were better than others and that some innovations were obviously desirable, so that most systems came to have certain features in common. The system with which I was associated, the Missouri Automated Radiology System (MARS), went on line at the University of Missouri-Columbia School of Medicine (Columbia, Mo) in April of 1970[11] and underwent constant modification until it became an extremely useful system. In 1974 the cost-effectiveness of MARS was the subject of a detailed economic analysis,[12] following which the hospital assumed financial support of the system. A major element of the continuing success of MARS was that the MUMPS programming language permitted on-line modification without interrupting function. Hence, MARS was kept up-to-date.[13] For all systems, a rapid turnaround of reports was the problem least easily resolved[14-17] and often is a problem today. For film tracking, Bauman's use of bar coding has proved successful.[18]

It is a truism that a well-designed and supported radiology information system (RIS) becomes an instrument of management policy. It is equally true that, to be successful, a RIS must have the support of the chief of the department of radiology and, in a hospital, of the director of the hospital. A personal anecdote provides an interesting reflection on the value of a RIS. After more than 20 years as Chair of the Department of Radiology at the University of Missouri, I decided that I had achieved about all that I could as manager and retired to research and writing. My successor apparently ran into some of the insoluble issues that had plagued me during my tenure and ultimately gave it up. Not without some concessions by the dean and the University Hospital, I took on the responsibility again and was quite pleased to find that within a week it was possible to generate five-year charts showing patient volume, mix, financial trends and time flow—in short, all the information necessary to resume planning for the department's future. In my absence, the computer had been quietly ticking along, "faithfully" collecting all of this information that simply awaited analysis. I do not see how a large department can be managed effectively without an RIS. James Lehr, MD, who has redesigned MARS for the University of Chicago's Pritzker School of Medicine,[19] has written comprehensively on RISs.[20] The formation of the RIS Computer Consortium[21] has led to a systematic implementation of DECRAD, a state-of-the-art information system, which is being widely implemented. Many other RISs are now being marketed.

The Radiology Image Information System

With the flow of digital images into the clinical environment having been initiated and with the success of RIS as a model, we began to examine the possibility of implementing an image information managing system.[22] By 1977 digital image management had become enough of a problem that Hill and Jost were implementing data compression for more efficient archiving of CT findings.[23] A major stimulus to giving serious consideration to such digital systems has been the promise of mass storage devices for archiving digital data, particularly the digital optical disc. This festering problem of storing voluminous digital image files without systematic access added a sense of urgency to planning and implementing the new image management system. Implementation has been slow for many reasons, however, a major one being that industry is still not geared to the task of producing a system for storing, retrieving, transmitting and displaying digitally acquired radiographic images within the constraints of speed, spatial resolution and human engineering imposed by the radiologist users. At the same time, radiologists have not had hard data to answer many questions related to the design specifications of the proposed system. Many questions will eventually be resolved by research with human subjects, some others by trial and error and all ultimately by the marketplace.

The design and implementation of an image information management system is a massive scientific effort, the successful implementing of which will have an impact far beyond the perimeters of radiology. Accordingly, as a systems problem, it will not be rapidly resolved, but, rather, success will in large measure depend on simultaneously solving tough technical problems now under intensive study. Many of these are beyond the normal expertise of radiologists, while others can be solved only with the professional guidance and collaboration of radiologists. A number of recently published review articles have illuminated the technical scope of the image management system and the progress that has been made.[24-26] Several problem areas are briefly discussed below.

The Financial Atmosphere

The desire to contain costs and the change in methods of reimbursing a radiology department to charging costs against a total predetermined by federally imposed diagnosis-related

groups has placed us in the position of needing to design a system that diminishes operating costs. The economics of PACS has been examined,[27,28] but as yet we do not have a good enough model to show that PACS can compete economically with current film systems. We have not been able to afford to implement those models of systems that incur major costs for displays. As of now, several systems for creating digital x-ray images are being extensively tested in Japan, based on the Fuji technology, which acquires images digitally from plates but captures the digital information on film. This technology permits bypassing the costs of digital storage, networking and displays. Such systems are only one component of the image management system but can be plugged into an existing department without requiring a major change in a radiologist's routine and possibly without major change in operations or costs. While these systems tend to perpetuate film-based departments, they will satisfy the radiologists' traditional demand for film images. The Fuji plate technology represents a technologic breakthrough for generating high-resolution digital images and undoubtedly will accelerate the conversion to the digital department.

The ACR-NEMA Digital Interface Communications Standard

The design specifications of most digital imaging equipment do not include standardized output signals. The result of this is that if image signals are to be transmitted on a network or displayed on another manufacturer's equipment, a special interface must be designed to make the original image signal interpretable. In a major departure from the past, the users of radiologic imaging equipment, represented by the American College of Radiology (ACR), and the manufacturers of imaging equipment, represented by the National Electrical Manufacturers Association (NEMA), have formed a joint committee, with its first task to specify a standard interface for the transfer of digitally formatted images. In just two years this committee and its working groups have created an industry standard interface, ACR-NEMA Digital Imaging and Communications Standard, publication No. 300-1985, available from the National Electrical Manufacturers Association, 2101 L St NW, Suite 300, Washington, DC 20037. The interface specifies the lower four layers of the ISO-OSI seven-layer reference model.[29] The standard specifies a 16-bit parallel interface with six control signals. Data rates of 8 megabytes can be achieved over a cable of 15 m maximum length. The standard is now being implemented by various manufacturers and other interested parties. Working Group 4 of the ACR-NEMA Committee will shortly present its recommendations for a tape interface standard, and approval is expected by the end of 1986. Under study are plans for accommodating various compression algorithms with the interface standard and for transmitting three-dimensional images through the standard interface. Working Group 6 serves to help validate the standard. The ACR-NEMA Committee will continue its function for the foreseeable future, upgrading the standards as required. A comprehensive analysis of the interface standard is being prepared for publication in 1986.[30]

The Digital Workplace

Of all of the elements of a digital image management system, the display is perceived as most problematic. This is because it must be designed to replace not just a set of illuminated view boxes but rather a complex system for efficiently presenting a preprogrammed day of work for radiologists, with as many images as necessary for thoroughly understanding each case. The rule is that the display must function at least as well as radiologists' present equipment or it will not be acceptable. Radiologists must be able to interrupt their examination of specific cases, look at images of immediate interest to referring physicians and easily resume their scanning of those cases. Images that are upside down or backward must be repositioned. Images must move rapidly and with precision: it must be possible to reposition images in closely aligned groups for ease of comparison. It should be possible to window CT scans or to call up images from another examination for comparison. The display must be a facile window into the image file of the institution. It must be possible to simultaneously review previous reports on a case under study or to annotate examinations where desirable. It should be possible to accomplish all of these maneuvers at a display screen time of 0.5 seconds or at a rate comparable to moving films by hand. And there should be the possibility of obtaining hard copies on film or paper.

The largest and most elaborate displays will need to present images at 2,048 by 2,048 squared pixels with 12 bits of grey-scale depth. Dwyer believes that a single display screen may suffice[25]—a debatable issue. Less elaborate displays may have less spatial resolution but can aecommodate by reviewing smaller areas of images of higher pixel densities and through zooming. So far, displays that fully meet the needs of radiology have not yet been marketed, and the prototype models have been prohibitively expensive. A generic display with the features of a high-level work center, versatility and more is under development in the radiology department at Massachusetts General Hospital (R-Star). Many others are also under development.

Data Compression

Given the high data rates and the huge storage eapacities required for archiving and rapid transfer of digital images, methods for reducing data volume are of great interest. Each digital image contains information that is redundant in that it does not contribute to the diagnostic content of the image. Some images contain a great deal more redundant information than others. Contrast level redundancy refers to patterns of repetition in the degree of pixel brightness. Huffman encoding is a commonly used method of providing contrast compression through estimating the probability of occurrence of pixel contrast values.[31] "Lossless" encoding permits image data compression that is not subject to loss of information. The amount of image compression that can be achieved without loss of information, however, is relatively small, such as 2:1 or 3:1. Other compression techniques extend to 20:1 or higher, but with nonrecoverable loss of image information. Image decompression times are also a significant issue because the time required for decompression may be many times longer than that required for the initial compression.

At this point, if images can be compressed at high rates without losing diagnostic quality, this would make the image transmission, archiving and retrieval times much faster and less expensive. Because of this economy, image data com-

pression has become a very important issue but one that can only be finally solved by experimentally determining which algorithms can provide the greatest time and cost benefits without significantly degrading diagnostic quality.

The Local Area Network

Computer networks are an essential part of the digital image management system. The twisted wire networks are far from fast enough for image transmission purposes, and coaxial cable provides a marginal top signaling rate of 60 megabits per second.[25] It seems very likely that future transmission needs will be met only through the use of fiber-optic cables, which will provide a signaling rate of more than 200 megabits per second. While few departments are now using networks for image transmission, many are installing cables, often both coaxial and fiber-optic cables.

It should be noted that the data-signaling rate is much higher than the actual rate of data production, the difference being due to overhead such as the size of records being transmitted, the size of buffers and the number of active nodes on the network.[25] Obviously, image data compression is an extremely important variable in improving the data-production rate of PACS networks.

Archiving and Data-Base Management

In radiology departments today, digital images are stored on magnetic tapes and discs, usually in files that often are remote from the active department. Film copies of digital images, such as CT, magnetic resonance images and ultrasonograms, are filed in a master folder in the film library. If the film copies of CT images are lost, the magnetic media are withdrawn from storage and are scheduled into the patient queue for access to the CT scanner, where they are rephotographed. This process takes 24 hours or longer under any but urgent circumstances. Archiving of digital images on mass storage media such as optical disc or tape storage clearly is desirable, but for mass storage to exist, there must be mechanisms and demands for accessing mass storage. There must be data transmission networks, imaging devices that feed the transmission networks and workstations for accessing and displaying the digital images that are filed in mass storage. We have a chicken-and-the-egg situation; you cannot have a part without the whole. These systems are generally not available except as prototypes. Noz and co-workers recently surveyed PACS systems, mostly in universities and in large hospitals, to find that some prototype systems are centralized and others decentralized.[24] In a centralized system, every image that goes onto the network gets sent to the image archiver or file server. All requests also go through the central archive. The decentralized system may have local magnetic disc archives and a ring or star configuration, so that images and messages can be sent directly to other points on the network without going through a central archive. Raytel markets a PACS that offers two digital optical disc archives featuring multiplayer laser optical disc "jukeboxes." These disc stores have a four-second response time to search, load and spin to an image. The PACS offered by Raytel is based on a centralized topology. Generally, however, massive storage is still a part of the prototype development that is now going on. Data-base management systems are a part of this development.

Discussion

Those who have been participating in the development of the radiology image management system can see that all of the parts of the system are inevitably being assembled. The question is when they will all be put together and start being used as a system. We can see that this is happening in a limited way now, largely in university settings using manufacturers' prototypes. The manufacturers of imaging equipment have assembled PACS research and development teams and are looking at the marketplace, measuring radiologists' enthusiasm, seeking opinions from the experts and hedging their bets on the future. A PACS is big money. A well-informed guess is that the image information systems will move off center and gain momentum when the proportion of digital images to film images reaches 50%. As of 1984, the evidence is that the volume of digital imaging at Massachusetts General Hospital was 20% of the whole and that plain film images comprised the remaining 80%.[2] This would indicate that 30% of film images would need to be converted to digital format before the system would begin to take off.

As of now, the major viable large-volume source of high-resolution digital images that would replace standard x-ray film images would appear to be from the clones of the Fuji imaging plate system now being produced in Japan and Europe. If this proposed algorithm of 50% replacement is correct, we will know when the time has come by watching the sales of imaging plate technology. Money must be available, however, for the larger health care institutions to buy such technology, which means that there will need to be enough savings to make these systems attractive. Given this scenario, it can be anticipated that we will be well into the 1990s before operational image management systems are a significant factor in improving the quality of radiologic practice. In the meantime, the component systems will be polished and, with current trends, the prices will diminish.

Conclusions

After nearly 20 years of development, radiology information systems are now routinely used in large departments. Still incompletely resolved is the reporting function, where the equivalent of direct dictation and transcription is desirable. Voice recognition has been tested but not yet proved sufficiently reliable.[32] Coded reports, direct entry by radiologists, telephone access to dictated reports and tightly coupled transcription pools are all solutions that await a better one.

What is to be the future of the RIS in the presence of the PACS system? RIS covers a broad spectrum of functions that support but are not a direct part of image management. Lehr believes that the implementation of PACS should probably be considered as a replacement of the film-file-management module of an RIS.[33] PACS could not survive in an environment without the RIS function. The evolution of PACS will inevitably include the fusion of the two systems.

The future implementation of PACS appears to depend on establishing in radiology departments a cost-effective digital replacement of the standard x-ray image. It can be predicted that radiologists will give up film images with great reluctance. For this reason the systems that are based on the Fuji imaging plate principle, producing either a digital x-ray film or, alternatively, an image on a high-resolution screen, ap-

pear to be the most viable candidates for replacing the standard x-ray image.

Economics will remain a major issue. If the imaging system can be shown to speed the process of inpatient care, save money through providing efficiencies in film production and management and, particularly, if systems are interfaced with hospital systems and inform hospital administrators as to how radiologic resources are used, then money will be found to support their purchase. It is not so much whether society can afford information management systems as whether it can afford not to have them.

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Bringing the Medical Literature to Physicians

Self-Service Computerized Bibliographic Retrieval

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Seven years ago physicians at the Beth Israel Hospital in Boston began doing their own searches of the medical literature. They used PaperChase, a computer program written especially for end users rather than for search librarians. The data base was initially limited to the journals shelved in the library of the Beth Israel Hospital, but it has since been expanded to include the entire MEDLINE collection of the National Library of Medicine—nearly 5 million references published in 3,400 biomedical journals dating back to 1966.

PaperChase is now available throughout the United States and Canada to anyone who has a computer terminal or personal computer and a modem. No special training is needed for a successful search and there is no user's manual. Users can search by title word, "medical subject heading," author's name, journal title, year of publication, language of publication or any combination of the above. They can read abstracts on line, and they can request that a photocopy of the full text of any article be mailed to them.

(Underhill LH, Bleich HL: Bringing the medical literature to physicians—Self-service computerized bibliographic retrieval, *In* Medical informatics [Special Issue]. West J Med 1986 Dec; 145:853-858)

All medical schools and many hospitals have medical libraries. Libraries catalog books by author, title and subject and usually shelve them according to the organ system or medical specialty to which they pertain. Journals, however, are another matter. They cannot be catalogued or shelved by subject or author. The table of contents in each issue and the subject and author indexes at the backs of bound volumes are not particularly helpful to a person who wishes to look up specific subjects or authors without regard for the year of publication or the journals in which they may be found.

About 100 years ago, while working on his medical-school graduation thesis, John Shaw Billings conceived the idea that led to *Index Medicus*.[1] Now published by the National Library of Medicine, *Index Medicus* permits readers to look up articles in a given year by author or by Medical Subject Heading. To look up information over a period of years, however, many hefty volumes must be consulted. More important, there is no convenient way to find articles common to two or more Medical Subject Headings. One can find articles about liver disease and those about congestive heart failure, but manual cross-referencing is required to find articles that discuss both.

The solution to this difficulty is to have a computer program with the capability to cross-reference. Most medical schools and many hospitals now have specially trained reference librarians who use computer programs to search MEDLINE, the data base from which the printed volumes of *Index Medicus* are derived. MEDLINE is the largest and by far the most popular of the computerized data bases of medical literature maintained by the National Library of Medicine. In addition to the National Library of Medicine, Bibliographic Retrieval Services (BRS)/Saunders Colleague and Dialog also provide computer programs that permit specially trained reference librarians to search MEDLINE and other data bases. More recently, the National Library of Medicine, Mead Data Central, BRS/Saunders Colleague and Dialog have begun to offer more user-friendly approaches to the MEDLINE data base.

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These programs meet many of the needs for computerized bibliographic retrieval of the biomedical literature. Nevertheless, because they require either the services of a specially trained reference librarian (who is usually available only during the day by appointment) or much special training, mastery of complex users' manuals and practice with the search procedure, they are often unsuitable for medical students, house officers, nurses or practicing physicians with an urgent clinical problem. For these people, most of the information in a hospital library can be retrieved only with considerable effort.

How PaperChase Began

Many years ago our clinical computing laboratory developed a literature-retrieval program to help find references from the reprint collection in our department.[2] At that time we had about 12,000 reprints, most of which pertained to our research interests or to topics in general clinical medicine. The ability to search this data base rapidly and to obtain useful references immediately was for us a new and valuable experience. One day a medical student on rotation through our laboratory suggested that we deploy a similar facility in our hospital library. Several features seemed essential for a program of this sort.[3]

First, the program should be self-service. The need for a user's manual or for a librarian intermediary seemed incompatible with the requirements of a busy hospital, where a user's first encounter could occur under conditions of medical urgency.

Second, the terminal should be located in the hospital library and, like the library, should be available round-the-clock.

Third, the program should accommodate all of the references shelved in the hospital library. If additional references not shelved in the library were included in the data base, they should be displayed last and at the option of a user.

Fourth, a user should never lose data. A user who is called away during a search or who abandons a terminal in the midst of a search should be able to resume from the same point later.

Fifth, computer-response time, even for a complex search, should be rapid; for a busy clinician, delays of even a few seconds are often considered unacceptable.

PaperChase was designed with these principles in mind, and the first version was installed in the library of Beth Israel Hospital seven years ago. The data base for PaperChase was taken from computer tapes prepared for us by the National Library of Medicine. Originally it consisted of approximately 400,000 references from 258 journals, dating back eight years—nearly all of the references shelved in the library of the Beth Israel Hospital. Today PaperChase contains all references indexed for MEDLINE since its inception in 1966—nearly 5 million references from more than 3,400 journals. Two years ago the program was made available to outside subscribers and it is now widely used throughout the United States and Canada.

How PaperChase Works

To interact with PaperChase, a user need not learn special commands or remember special formats for entering data. PaperChase is menu-driven. If at any point a menu is unclear, entering a question mark summons on-line help. No previous training is necessary, and we have never found it necessary to write a user's manual.

Searches may be conducted by title word (any word in the title of an article), Medical Subject Heading or Subheading (terms used by the National Library of Medicine to index, or classify, the biomedical literature), author's name, journal title, year of publication or language of publication. Lists of references that meet these specifications can then be crossed, combined or subtracted to create more specific lists. Once a list has been made, the references on that list can be displayed. If a reference is of particular interest, it can be selected for printing at the end of the search. In addition, its abstract can be displayed or printed. If the reference is of particular interest, the user can request a photocopy of the full text of the article, which will be delivered by mail.

Finding Things With PaperChase

To help users find topics, PaperChase automatically unifies nearly all spelling variants, plural forms, hyphenated words, punctuated words and other grammatically related forms; a search for any form of a word will ordinarily locate all of the others.[4] When a user is unsure of an exact spelling, only the first portion of any entry need be used. The need to type only initial letters is particularly helpful for drug names, such as dichlororibofuranosylbenzimidazole (a Medical Subject Heading), which few people can spell correctly. It also saves time.

Throughout a search, PaperChase helps guide the user. Search specifications can be entered in almost any reasonable format. For example, in the MEDLINE data base, authors' names are stored in the form SMITH JW; if a name is entered in another form, such as JW SMITH or SMITH, JANE W, PaperChase will translate the user's entry into the form used by the National Library of Medicine. Journal titles can be entered in full, or they can be abbreviated in virtually any way that a user wishes. For entries that match more than one journal, PaperChase will display all possibilities and ask the user to choose the correct one. To search by year of publication, a user types the year desired, and PaperChase then provides the option to search under that year or under a range of years starting with the year specified. References published in a particular language can be found by typing the name of that language.

The ability to locate authors, journals and Medical Subject Headings without knowing the accepted form and to locate all entries by their initial letters is a big help to our users, many of whom type with considerable reluctance and spell with remarkable imagination.

PaperChase also monitors users' search strategy and continually offers suggestions for improvement. For example, if a user selects a title word, PaperChase will try to guide the user to a related Medical Subject Heading instead. In some situations, such as when an article is known to contain a particular word in its title, the user may elect to search by that title word. But in most cases, a search based on one of the 14,000 carefully standardized, hierarchically organized Medical Subject Headings is more likely to be complete than is a search based on one of the 200,000 title words in the data base.

For example, a search by the title word IDDM (insulin-dependent diabetes mellitus) yields 58 references; by contrast, a search based on the Medical Subject Heading DIABETES

MELLITUS, INSULIN-DEPENDENT yields 7,631. Because of the importance of searching by Medical Subject Headings and because the typical user has no way to know which words or phrases the National Library of Medicine has chosen for its Medical Subject Headings, PaperChase offers a user who chooses a title word the option of replacing it with the Medical Subject Heading. Thus, a user who types IDDM is given the option of replacing it with DIABETES MELLITUS, INSULIN-DEPENDENT, and the user who types CME the option of replacing it with EDUCATION, CONTINUING, MEDICAL. The ability to point a user from title word to Medical Subject Heading automatically, a feature unique to PaperChase, is widely considered to provide users of PaperChase with a major advantage over users of other programs that search the MEDLINE data base.

In addition to its ability to point a user from title word to Medical Subject Heading, PaperChase helps users find Medical Subject Headings in other important ways. A user who types a Medical Subject Heading, such as ARTHRITIS, is automatically offered a choice of alphabetically related Medical Subject Headings, such as ARTHRITIS, INFECTIOUS; ARTHRITIS, JUVENILE RHEUMATOID, and ARTHRITIS, RHEUMATOID. Sometimes the choice of one of these related terms yields a more specific or a more complete search.

A user who types a synonym for a Medical Subject Heading is automatically pointed to the proper term.[4] Thus, the user who types VITAMIN C is automatically given ASCORBIC ACID; the user who types CRIB DEATH is automatically given SUDDEN INFANT DEATH SYNDROME. If a Medical Subject Heading contains the word AND, it is also listed with its phrases reversed; thus, the user who types REAGENTS finds REAGENTS AND INDICATORS but is automatically given INDICATORS AND REAGENTS instead. Finally, PaperChase permutes all multiword Medical Subject Headings. Thus, the user who types SYSTEMIC LUPUS finds SYSTEMIC LUPUS ERYTHEMATOSUS but is automatically given LUPUS ERYTHEMATOSUS, SYSTEMIC; the user who types CREUTZFELDT-JAKOB DISEASE is automatically given JAKOB-CREUTZFELDT DISEASE. Of all the systems that search the MEDLINE data base, only PaperChase provides users with so much help in finding Medical Subject Headings.

Focusing a Search

A search of the MEDLINE data base sometimes produces too few references, sometimes too many. When it produces too few, PaperChase uses two techniques to help a user find additional Medical Subject Headings that can be used to broaden the search. First, it offers the user Medical Subject Headings that are medically related to those already chosen. Medical Subject Headings are hierarchically organized; by automatically suggesting headings that are above and below the chosen one in the hierarchy, PaperChase provides a user who finds too little under HEADACHE the chance to broaden the search to include the more general term, PAIN, as well as the more specific terms, MIGRAINE HEADACHE, CLUSTER HEADACHE and TENSION HEADACHE.

Second, when a user displays a reference, typing a "P" places that reference on a queue for printing at the end of the session. We believe that a reference selected for printing is more relevant to the user's needs than is a reference displayed but not so selected. Accordingly, PaperChase tallies the Medical Subject Headings from each reference selected for printing and reflects back to the user those that occur most commonly. Thus, the user who makes a list of references common to the terms PNEUMONIA and STREPTOCOCCUS PNEUMONIAE and who selects for printing those references that deal with therapy receives for consideration a list of Medical Subject Headings that includes MINOCYCLINE, MICROBIAL SENSITIVITY TESTS and PENICILLIN RESISTANCE. By contrast, a colleague who displays the same references but who selects for printing those that deal with diagnosis receives a list that includes BACTERIOLOGICAL TECHNIQUES, PRECIPITIN TESTS, IMMUNOELECTROPHORESIS and COUNTERIMMUNOELECTROPHORESIS.

If a search elicits too many references, PaperChase suggests several ways for the user to cut it down. When a user displays a long list, PaperChase suggests that the user limit the search to review articles or to articles published in recent years. In addition, it suggests that Subheadings, terms chosen by the National Library of Medicine to qualify Medical Subject Headings, be used to cut down the list. For example, if a user displays a list of references that discuss NIACIN, the Subheading ADVERSE EFFECTS can be used to limit the display to articles that discuss the side effects of niacin administration. PaperChase permutes Subheadings and recognizes them by their synonyms and by their initial letters; thus, a user need not be familiar with these terms to use them effectively.

Using PaperChase

There are two major displays in PaperChase. One is "LOOK FOR" and the other presents a series of "options." At LOOK FOR the user may type a title word, a Medical Subject Heading, a Subheading, an author's name, a journal title, a year of publication or a language of publication. If the user enters a word, such as BONE, that could define a Medical Subject Heading or title word, an author's name or a journal title, PaperChase will ask the user which option was intended.

Each time a user selects a search term, a list of references is created that meets that specification. After one or more lists have been created, the user proceeds to the second major display in PaperChase—the list of options. These options enable the user to combine lists, find references common to two or more lists and view references on a list—either in abbreviated form by scanning their titles or in a more complete display that includes all authors' names and a list of the Medical Subject Headings under which each article has been indexed.[5]

A Typical Search

Suppose a user is interested in the computed tomographic scan to diagnose Alzheimer's disease. The user could begin by typing CAT. The program would then respond with a numbered menu of title words and Medical Subject Headings for which CAT are the initial letters (Figure 1). In this case, the user would choose item 5, * CAT SCAN, X-RAY. Choosing this item results in the instantaneous availability of 27,892 references that have been indexed under the Medical Subject

Heading TOMOGRAPHY, X-RAY COMPUTED, for which CAT SCAN, X-RAY is a synonym.

Having obtained a list of references that discuss CAT SCANS, the user could then type ALZ for Alzheimer's disease. Because ALZ is the initial fragment of both an author's name and a title word or Medical Subject Heading, the user is asked which of these is intended. When the user chooses "Title Word" or "Medical Subject Heading," the program responds with a numbered menu of title words and Medical Subject Headings that begin with ALZ—a menu that includes ALZHEIMER, ALZHEIMER'S DISEASE and ALZHEIMERISM. In this case, the user chooses ALZHEIMER'S DISEASE.

Having created the two desired lists, the user proceeds to the display shown in Figure 2. By selecting option 5, "Find References Common to 2 or More Lists," the user instructs the program to examine each reference on list A, to see if it is also present on list B and, if it is, to put it on a new list, C. The computer may require a number of seconds to complete this new list, but the first reference can be displayed as soon as it is found. By the time the user has studied the first reference, the computer has almost surely found several more; as a result, the user seldom perceives delay.

Each display includes the authors, title, journal, volume number, page numbers and year of publication (Figure 3). Also included are the major Medical Subject Headings under which the article has been indexed (the principal topics discussed in the article and the only ones found in *Index Medicus*), followed by the minor terms. The display of Medical Subject Headings provides the user with an indication of the article's contents (Figure 3).

If a reference seems pertinent, the user can type an "A" to read its abstract, a "P" to select that reference for printing at the end of the session and a "C," for copy, to request that a photocopy of the full text of the article be sent in the mail. After a list has been viewed and references have been selected for printing, PaperChase offers the user additional related Medical Subject Headings with which to expand the search (Figure 4).

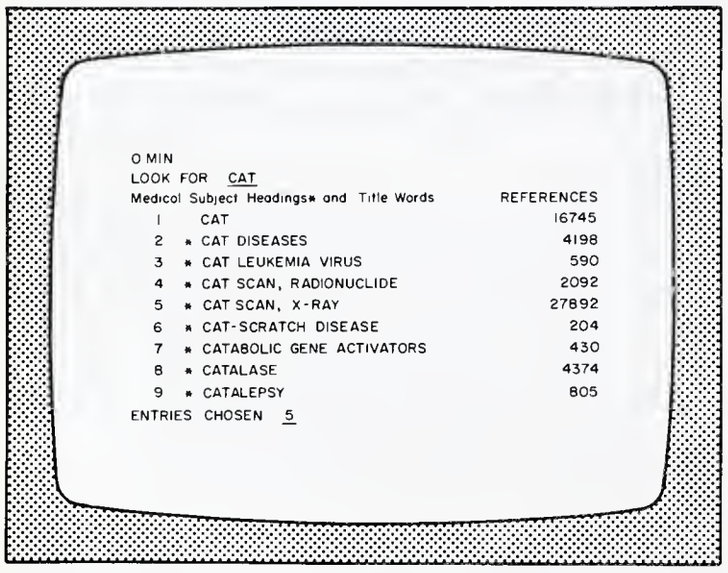

Figure 1.—A computer-screen display is shown of the response to "LOOK FOR: CAT." Terms that were underlined were typed by the user. All other information in the display is provided by PaperChase in response to the user's entry. Medical Subject Headings and their synonyms are distinguished from title words by asterisks. In this display, item 5, CAT SCAN, X-RAY, is a synonym for the Medical Subject Heading TOMOGRAPHY, X-RAY COMPUTED. By choosing item 5, the user creates a list of 27,892 references (indicated by the column on the right)—all of the references in the MEDLINE data base going back to 1966 that are indexed under this Medical Subject Heading.

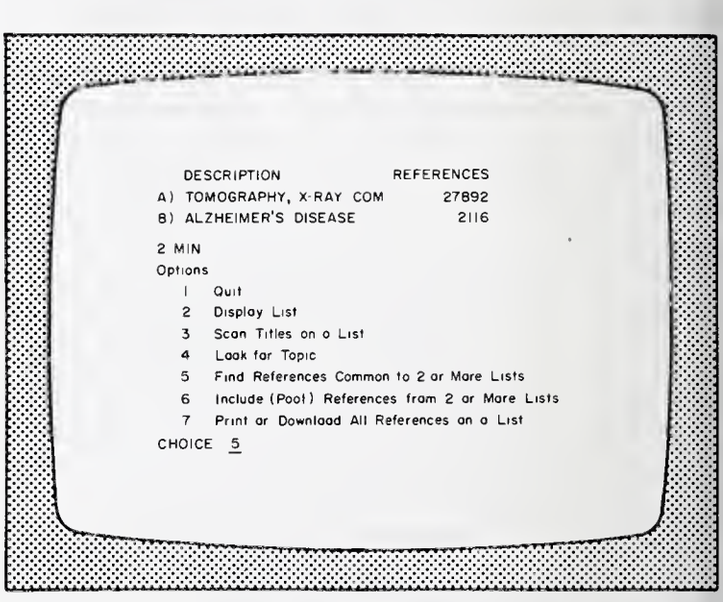

Figure 2.—A computer-screen display is shown of the PaperChase options after two or more lists are created. This display shows the two lists that the user created in the sample search discussed in the text. The upper portion of the screen can accommodate as many as 18 lists, each of which is referred to by the letter that precedes it. There is no limit to the number of lists that can be created. The lower portion of the screen contains the options that can be used to manipulate lists; options 5 and 6 permit the user to effect Boolean operations. By choosing option 5, the user creates a new list, C (not shown), that includes all references common to lists A and B.

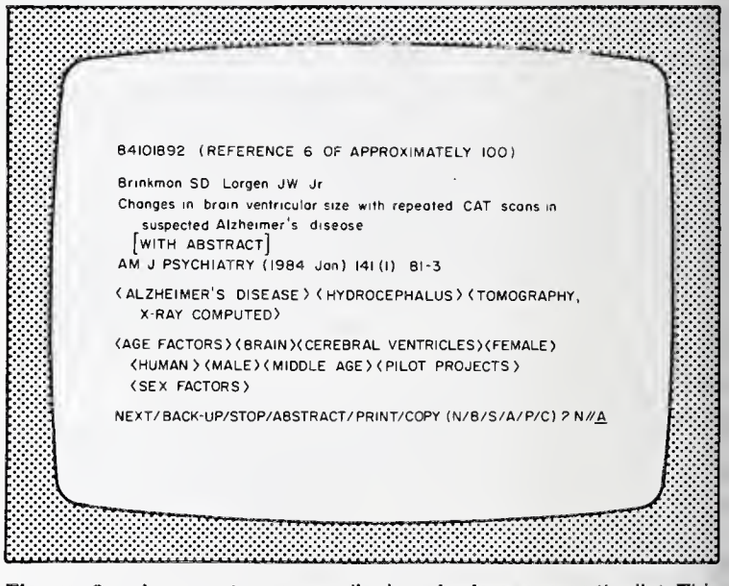

Figure 3.—A computer-screen display of references on the list. This display shows one of about 100 references that are indexed under both of the Medical Subject Headings TOMOGRAPHY, X-RAY COMPUTED and ALZHEIMER'S DISEASE. The number in the upper-left corner is assigned by the National Library of Medicine. To proceed to the next reference on the list, the user just presses the return key. By typing an A, the user can view the abstract for this reference; a B causes PaperChase to go back to previous references; a P puts this reference on a queue to be printed at the end of the session, and a C requests a photocopy of the full text of the article to be mailed to the user. At the end of the search, the user can review items selected for printing or photocopying and delete any that no longer seem of interest.

References selected for printing are printed at the end of the session in alphabetic order by journal title, the way they are likely to be shelved in a library. Requests for photocopies are relayed electronically to the College of Physicians of Philadelphia, where 80% of the articles requested before 8 AM are mailed that afternoon.

As the user signs off from PaperChase, there is an opportunity to leave a message or comment. PaperChase experts read each message and try to respond to questions within 24 hours. Many ideas for improving PaperChase come from our users, to whom we are much indebted. The most frequent comment is THANK YOU (sometimes misspelled). One of the more favorable comments came from a medical student who learned through PaperChase that long-term lithium carbonate therapy can induce a pattern of abnormalities characteristic of primary hyperthyroidism.[4] He wrote that PaperChase probably saved his patient from a longer stay in hospital and a parathyroid operation.

One of the most unfavorable comments came from a senior faculty member of our medical school who tried to look up articles written by a colleague. When he misspelled the colleague's name, PaperChase found nothing. He wrote "useless" and did not return to PaperChase for many months. Now, however, he is a regular user.

The Search Is an End in Itself

Users of PaperChase often find the information they seek without consulting bound volumes. The titles of articles in medical journals are often short medical statements, and the information they provide, combined with the display of associated Medical Subject Headings, is often sufficient to answer an important medical question.[6] If the information is not found in the title of the article, it may be in the abstract, which can also be displayed on line. And if more detail is required, PaperChase permits the user to order a photocopy of the full text of any article in the data base.

A house officer at our hospital once wanted to know if transitional cell carcinoma of the urinary tract was associated with the overuse of analgesics. After spending a few minutes with PaperChase, he found five articles whose titles strongly suggested such a relation.[7-11] At this point, he did not know the frequency of the association, the amount of analgesic (phenacetin) required to induce a carcinoma or whether a critical appraisal of the literature would indeed confirm the association. Yet, he did know that at least five articles in refereed journals stated that such an association existed.

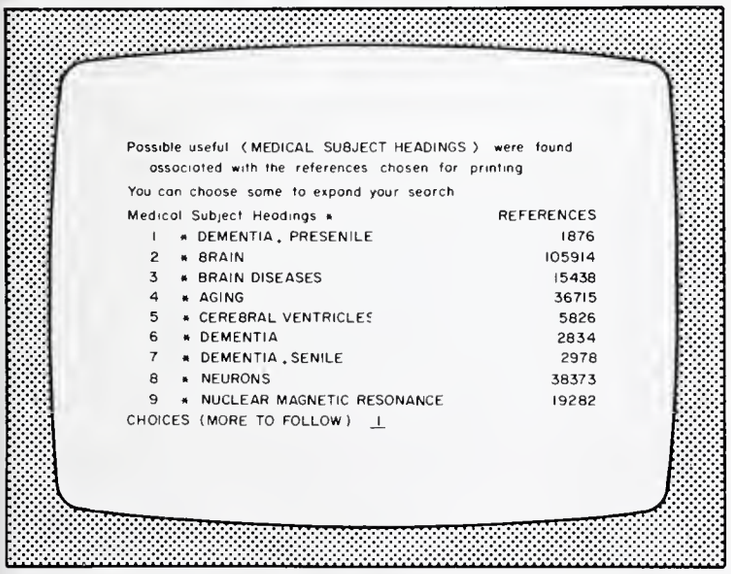

Figure 4.—A computer-screen display is given of additional Medical Subject Headings. After a List has been displayed, PaperChase offers the user a choice of additional Medical Subject Headings with which to broaden the search. These terms are chosen on the basis of the articles selected for printing or photocopying. The display reproduced here is one of many that might result from the search described in the text and depicted in Figures 1 to 3.

On another occasion, jaundice developed in a patient shortly after he began taking methyldopa for the treatment of hypertension. His physician wanted to know if the methyldopa could be the cause of the jaundice. Using PaperChase, the physician searched for recently published references that dealt with METHYLDOPA and either LIVER, HEPATITIS, or JAUNDICE. In all, 33 references were found and from their titles the physician learned not only that methyldopa can induce jaundice, but also that several forms of liver injury are possible, including hepatic necrosis, granulomatous hepatitis, postnecrotic cirrhosis and cholestasis. He also learned that in some cases the liver damage progresses to fulminant hepatic failure. And, with no extra effort, he learned that methyldopa has been thought to cause colitis, myocarditis and carcinoma of the biliary tract. Had the physician chosen to read the abstracts of these articles, his use of PaperChase could have been even more instructive.

Advantages of Self-Service Bibliographic Retrieval

The ability to do one's own searches permits them to be done at the users' convenience. In addition, most users find that doing the search is both enjoyable and educational.

While doing a search, users often discover ideas and information that can then be incorporated into the search to make it more useful and pertinent. The ability to incorporate feedback into the search immediately is an important feature of self-service bibliographic retrieval. Users often find that their original question cannot be answered as they thought or that it leads to a more important question. For a user whose aim is unclear, information presented during the search sometimes suggests new and fruitful avenues of investigation. When an intermediary conducts the search, the flexibility to change direction and respond to information displayed is reduced. Many users have left comments to the effect that never again will they delegate their literature searches to anyone else.

Individual and Institutional Subscribers

PaperChase is available to persons and to institutions. In the case of an institutional subscription, a librarian or institutional representative can control access to the PaperChase. Access codes, issued by the institution to individual users, can be made to expire after a single use, after a period of time or after a predetermined dollar value has been exceeded. Management features permit librarians to monitor the search strategies of users and to review and reply to their comments.[5]

PaperChase allows a librarian to specify institutional holdings. Thereafter, users first obtain references available in that institution, followed, at their option, by the references that remain. In the case of an individual subscription or an institutional subscription for which indication of institutional holdings is inappropriate, the user first obtains references in

journals recommended by the American College of Physicians, *The New England Journal of Medicine,* Brandon and Hill, the Priority 1 *Index Medicus* journals and those most frequently cited in Year Books. In our experience, institutional holdings, or recommended holdings, are a particularly helpful filter, for they reduce the likelihood that a user will be overwhelmed by a large number of references. As a result, a broader search strategy can be used and a better search done.

Advanced Features of PaperChase

PaperChase offers a number of advanced features that may be of help to experienced users and reference librarians. For example, an experienced user can bypass virtually all menus by the direct entry of commands. In addition, PaperChase respects the slash notation for Subheadings; to find references that discuss the history of hospices, a user may look for HOSPICES, look for HISTORY and qualify the former with the latter. Alternatively, an experienced user who knows the two-letter abbreviations used by the National Library of Medicine to locate Subheadings can type HOSPICES/HI and create a list of references right away.

To obtain a full citation from fragmentary information, a user can type an author's last name, followed by the year of publication, volume number and page. Thus, HOROWITZ,1981,305,924 will identify a reference about PaperChase.[3] If unavailable, either year, volume or page numbers may be omitted.

To explore the hierarchic tree structure of the Medical Subject Headings, a user may type the numerical designation used by the National Library of Medicine for a Medical Subject Heading. For example, typing D12.776.377.715 permits a user to enter the tree structure at "serum globulins." The user can then move up or down the hierarchy, depending on what items are selected.

Conclusion

Traditionally, a physician who wishes to search the medical literature for information on a particular topic has two options: a manual search, volume by volume, using *Index Medicus*, and, for a detailed or more complex search that requires cross-referencing two or more topics, consulting with a specially trained search librarian who uses computer programs to search MEDLINE or another data base. PaperChase permits physicians and other health care providers to search the medical literature themselves for references that meet their specifications. The program requires no previous experience or training. It can be used from any computer terminal or microcomputer and modem. It runs nearly 24 hours per day and is available throughout the country. In our view, PaperChase merits the consideration of any physician or health care worker who wishes to do his or her own searches of the MEDLINE data base.

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Medical Libraries and Computers

The Role of Medical Libraries in Medical Informatics

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The classic function of health sciences libraries is to build and maintain a knowledge base and to provide timely access to that collective memory for the purposes of learning, teaching, caring for patients, conducting research or managing an organization. The formats and representation of that knowledge base are changing rapidly, as are the methods and techniques for gaining access to information. Medical libraries have long used computers for cataloging and controlling records but are now shifting to acquiring, managing and distributing bibliographic and full-text information to local library "networks."

(Matheson NW: Medical libraries and computers—The role of medical libraries in medical informatics, *In* Medical informatics [Special Issue]. West J Med 1986 Dec; 145:859-863)

A world encyclopedia no longer presents itself to a modern imagination as a row of volumes printed and published once and for all, but as a sort of mental clearinghouse for the mind, a depot where knowledge and ideas are received, sorted, summarized, digested, clarified and compared. It would be in continual correspondence with every university, every research institution, every competent discussion, every survey, every statistical bureau in the world. . . . This Encyclopedic organization need not be concentrated now in one place: it might have the form of a network . . . it would constitute the material beginning of a real world brain.[1]

. . . It would be well not to underestimate the potential of technology. . . . whatever one man can dream, sooner or later another man can build.[2]

The potential of medical informatics is limited only by our imaginations. In time, a rational system for obtaining new information, relating it to existing knowledge, organizing it to support decision making and making it available quickly and usefully anywhere in the world will exist—and this information system, like Wells's world brain, will be our libraries. Such libraries will come to exist because of scientific imperatives, not because of technologic developments. Science does not advance by piling up information but by organizing and compressing it[3]—formidable intellectual tasks in aid of which technology has few tools to offer. These libraries may come to exist more quickly in the biomedical sciences than others, however, because of the technologic intensiveness of these disciplines and because of the leadership at the federal level by the National Library of Medicine (NLM), the National Institutes of Health and the National Science Foundation, among others. A significant barrier to rapid progress lies in the limited number of scientists trained in the disciplines of medical informatics.

The need to switch information, not documents, and to actively process information was forcefully expressed in two major documents more than 20 years ago. In 1963 the President's Science Advisory Committee stated, "The ultimate aim is to connect the user, quickly and efficiently, to the proper information and only the proper information."[4] Reporting to the Council of Library Resources, Licklider called for a meld of library and computer into a "procognitive system" that "will not only present information to people but also process it for them, following procedures they specify, apply, monitor and, if necessary, revise and reapply."[5]

The comprehensive electronic libraries of the future are likely to take longer than the next decade to develop because some very difficult intellectual problems must be solved in a number of crucial areas: *knowledge representation*—the expression of knowledge in symbolic form; *knowledge and data acquisition*—methods and techniques for building and updating knowledge bases; *cognitive processing*—the integration of knowledge and strategies of problem solving, and the *human and machine interface*—methods that allow humans and machines to be mutually comprehensible.

Using available technologies over the past century, libraries have created functional systems to manage these problems at the physical materials level. Over the past two decades libraries have concentrated on converting these manual record systems. National classification systems, cataloging codes, subject-heading dictionaries, indexing and abstracting

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ABBREVIATIONS USED IN TEXT

IAIMS = Integrated Academic Information Management System
ILS = Integrated Library System
NLM = National Library of Medicine
OCLC = On-line Center for Library Cataloging
UMLS = Unified Medical Language System

systems, interlibrary loan networks and union catalogs now exist in electronic form. Health sciences libraries have been in the forefront of these efforts, but the breakthroughs needed to manage actual information and knowledge depend on new, interdisciplinary research efforts in medical informatics.

In the meantime, libraries continue as eclectic reference centers and sources of knowledge in a number of formats—paper books and journals, audiotapes and videotapes, computer software, electronic textbooks, journals and data bases and so forth—that are organized to provide needed information in a timely fashion. That libraries and information services as presently constituted are underutilized is a problem librarians have struggled for decades to overcome. Use is almost exclusively determined by accessibility, and accessibility is a function of distance and effort. Studies show that library use is an inverse function of distance.[6] The same is true for communication. Regular and consistent communication decreases dramatically when people are separated by more than 30 m (100 ft). The "principle of least effort"[7] governs the use of services, not the quality of such services. In fact, Allen has predicted that "improving the quality or performance of a particular information service will not lead to increased use of the service."[6(p 186)] Consequently, the focus on mechanisms that provide easy and timely access must be foremost.

The speed, relevance and delivery mechanisms should improve dramatically over the next decade with advanced technology. These improvements will occur for at least three reasons: (1) publishers are moving towards distributing books and journals in electronic formats at the same time that personal computer use is intensifying, (2) libraries will purchase these new formats and train people to use them effectively, (3) librarians will collaborate with medical informatics researchers to develop first-stage electronic libraries that are comprehensive, integrated, information service systems supporting intellectual work.

The concept of a comprehensive, integrated information service system is emerging under different names: in businesses as information resource management,[8] in universities as Project Athena and Intermedia,[9,10] in research libraries as a comprehensive electronic service systems[11] and in health sciences libraries as Integrated Academic Information Management Systems (IAIMSs).[12] The facilitating technologies for using these systems are sophisticated and powerful workstations, integrated through networks with many different systems that retrieve and manipulate information.[13]

Computers in Academic Health Sciences Libraries

One excellent perspective on the development of computer systems in health sciences libraries is available,[14] but a full-scale review has yet to be written. In this brief overview some of the uses of computer technologies by academic health sciences libraries over the past 25 years are highlighted. No attempt is made to chronicle the extraordinary leadership and creativity of the National Library of Medicine or to trace the emergence of electronic bibliographic data bases or to discuss automation in general and university research libraries in particular, for which there are excellent sources.[15-17] My purpose is to describe the foundations of the next decade's developments.

There are three basic uses of computers in today's libraries. The first is to manage and control their collections of books, journals and other information resources. The second is for data-base searching and development. The third is for networking and providing information.

Library Management and Control Systems

Library management and control systems are analogous to business systems and hospital information systems. Providing ready access to a library's resources, whether large or small, requires efficient record control. On a daily basis libraries carry out thousands of individual transactions in buying and receiving materials, maintaining an inventory record, tracking the status of materials at all times and accounting for services rendered. Table 1 provides some indication of the size and scale of a year's activity in academic health sciences libraries.

Academic health sciences libraries began to use computers for library record control systems in the early 1960s. Two pioneering libraries—the Washington University School of Medicine Library under the direction of Estelle Brodman and the UCLA Biomedical Library under the direction of Louise Darling—began with serial control systems. Over the next 20 years, what started as single-function systems to record the receipt of individual journal issues evolved by 1981 into full-scale multifunction, integrated library control systems—the Bibliographic Access and Control System at Washington University (St Louis)[19] and ORION at UCLA.[20] "Integrated library systems" (ILSs) permit a number of functions to be done within a single system based on a master unit record. Thus, the record of a book purchase becomes the basis for the accounting, the catalog and the circulation record.

In the 1970s, thanks to standardization of bibliographic data records under the Library of Congress's machine-readable cataloging format and the arrival of on-line computer technology, libraries were able to share bibliographic data nationally, thereby eliminating the need for every library to create its own records de novo. The On-line Center for Library Cataloging (OCLC) system was operating in 1971 and

TABLE 1.—*Summary Operational Statistics of US Medical School Libraries 1984-1985 (N=126)**

Categories	*High*	*Low*	*Median*	*Aggregate Total*
Clients	15,000	344	3,976	531,520
Print volumes in collection	619,422	11,468	140,403	19,841,187
Print volumes added annually	16,241	643	5,573	744,537
Serial titles	6,765	390	2,100	295,215
In/out traffic	789,380	10,590	238,156	28,911,103
Collection uses	844,457	7,213	232,218	26,198,306
Interlibrary loans	42,887	257	8,501	311,932

*From the Annual Statistics of Medical School Libraries in the United States and Canada, 8th Ed.[18]

available through national dial access by 1974. By February 1976, 2 million records were in the system; 10 years later 13 million records are available.[21] Now when a library purchases a book, 90% of the time the book will already have been catalogued by another library and the record is available for reuse with little or no editing. Initially, libraries used the OCLC system to produce printed catalog cards and stored the digital records for later use. Thus, when local minicomputer-based library control systems began to appear in the early 1980s, many libraries were well positioned to replace the traditional card catalog with an on-line system.

The National Library of Medicine's ILS software provided the springboards for the full-scale automation of health sciences libraries that is happening today.[22] Like the NLM's earlier Teletypewriter Exchange Network of the Abridged *Index Medicus* experiment, which was instrumental in launching the on-line data-base industry, the ILS public-domain software spawned a new industry that has made it possible for medium-sized libraries to automate quickly and relatively inexpensively. The leading systems among health sciences libraries are the OCLC LS2000[23] and the Georgetown University Medical Center (Washington, DC) Library Information System.[24] In 1983 only a handful of the 126 medical school libraries were significantly automated and able to provide on-line access to their catalog records. By the end of 1987, nearly 40% will have achieved a significant level of automation. Due to the large size of university research libraries, their library control systems have developed differently and more slowly than health sciences libraries.

Data-Base Searching Services

When electronic data bases in medicine, science, engineering and technology emerged in the 1960s, there were no more than a few dozen bibliographic files. By 1976 there were more than 300 publicly available for on-line searching. In 1984 more than 2,800 electronic data bases offered electronic journals, textbooks, newspapers, numeric data bases and bibliographic files in virtually all disciplines through the services of more than 360 vendors worldwide. A handful of vendors provide the primary data bases in biomedicine at hourly prices ranging from $16 to $300 a connect hour.[25] The number of records contained in data bases has grown exponentially from 52 million to 1.68 billion in the past decade. (*ASIS* [American Society for Information Sciences] *Bulletin* 1986; 12:2).

Data-base searching has gone through phases mirroring the development of technology and its diffusion. Searching has moved from a centralized batch mode to a centralized on-line mode and on to a decentralized on-line mode, and has shifted from an institutional service to a personal activity. Before 1971 data-base searching was a batched process conducted at only a few sites. Libraries formulated search requests for their patrons, mailing them to a search center that did the coding and processing and mailed the results to the requester. The whole process usually took two weeks. In 1971 health sciences librarians formulated search queries and carried them out on line through direct access to the NLM computer. Between 1976 and 1984 librarians did most of the on-line searching using a handful of vendors. Users required search intermediaries for a number of reasons: access was not simple; search protocols are complex and subject to continual change; on-line charges are very expensive, and few people had experience with computer terminals, personal computers or telecommunications systems.

Today, now that access is easier and more people are familiar with the procedure, libraries are finding that more and more users prefer to do their own bibliographic searches.[26,27] Many use microcomputer software to do automatic log-on and transfer the search results into local memory units. Libraries are responding to this trend in a number of ways: first, by offering training in effective search techniques, and, second, by beginning to secure electronic data bases for on-premises use, either for local on-line network access or through compact-disk technologies.

Health sciences professionals exhibit a consistent information-seeking pattern, especially for keeping up-to-date. They skim a few authoritative general journals and the primary journals of their subspecialties. Capitalizing on this behavior, vendors such as Bibliographic Retrieval Service/Saunders Colleague and MEDIS are offering a number of journals for full-text on-line retrieval. Some of the major titles are *The New England Journal of Medicine, The Lancet, The British Medical Journal, Nature, The Journal of the American Medical Association* and nine other American Medical Association journals.[28,29] Whether this medium offers an adequate solution to the problem of keeping up-to-date with quality information is a question that has yet to be answered.[30–33]

Today's data bases will not be adequate for long. Knowledge will only continue to expand exponentially. By delivering bulk information more rapidly, they accentuate the need for information processing through selection and compression.

Library Networking

Thanks to the leadership of the National Library of Medicine, virtually all health sciences libraries, no matter how small, are part of a regional medical library network. The principal purpose of the network has been to facilitate access to the literature through an interlibrary loan system of participating resource libraries. Each year about 2 million loans of photocopies of articles or original works flow swiftly through the system.[34]

The communications technologies used have evolved from paper mailed forms, through the use of the Teletypewriter Exchange Network to current electronic mail systems. Printed union lists of journal title holdings have given way to a sophisticated electronic request routing system called DOCLINE. DOCLINE automatically sends a request from a library to the nearest library in the system holding the journal title. If the designated library is unable to fulfill the request for any reason, the request is automatically forwarded through a chain of libraries until it is either successfully completed or reported as unfillable.

DOCLINE is extraordinarily useful and will continue as the backbone of the national interlibrary loan system until superseded by readily accessible electronic journals. The system depends on libraries reporting their holdings in a timely fashion. Two additional features need to be developed. Libraries must be able to report holdings to the journal issue level if the system is to work optimally. Also, a way must be found to couple the very swift and efficient electronic location of a document with effective and inexpensive electronic de-

livery of the same, not only to the originating library but to the person who requested the document in the first place. Efficient and cost-effective facsimile-transmitting technology is urgently needed.

The library-to-library telecommunications linkages are being built rapidly. The electronic linkage between the library and its institutional users is yet to be created in most medical centers. It is towards this goal that the National Library of Medicine's IAIMS program is directed. The concept is to develop interconnections between and among many disparate files, such as patient medical records, the biomedical literature, clinical and research laboratory data, hospital information systems, drug information systems and so forth so that at any stage of decision making information can be drawn from relevant files. Significant economic, technologic and behavioral barriers confront those who hope to achieve this first-level linkage. Local telecommunications networks must be laid, the network architecture must accommodate heterogeneous hardware and software systems, file security must be assured, information files must be designed for effective use in an on-line problem-solving environment, the user community must accept and adhere to a set of system standards, training must be carried out and end-user technology must be ubiquitous and part of the fabric of everyday activity. Essentially, a network culture must emerge.

What Have Medical Libraries to Do With Medical Informatics?

For many in the field of biomedical library science, what role medical libraries play in the area of medical informatics is the burning question of the day and for the future. The answers to the question are not at all clear. The traditional domain of libraries has been the medical literature. Bibliographic indexes and catalogs have been the primary focus. Some libraries are moving into the business of electronically storing and retrieving the medical literature itself, as they have the paper formats. Further roles are on the horizon, however. Schoolman has suggested that if libraries "are to be relevant in supporting clinical decision making, they must be prepared to deal with a variety of new information attributes." Further, he says "they will have to develop access to and the ability to synthesize patient records and hospital management information systems."[35] Even more provocative is the idea that libraries should be responsible for the acquisition, storage and retrieval of the working papers exchanged by scientists exclusively over electronic network communications, which in some fast-moving fields is the equivalent to publication.[36]

Whatever the content of files, it is the storage, retrieval and delivery issues in medical informatics that are likely to involve librarians. For the near term, efforts may be concentrated on developing more intelligent means of access to bibliographic and factual data bases. Libraries will provide gateways to searching multiple external information data bases and they will acquire and manage bibliographic data bases, such as MEDLINE, the Institute of Scientific Information's *Current Contents* and specialized factual data bases, such as those on drug information, for distribution through local area networks. In some instances libraries will independently or collaboratively develop on-line data bases to meet local needs, such as creating directories or special subject bibliographies. Other libraries will begin to develop software that facilitates the use of many data bases and that links library-operated systems to users through networks or direct dial access.

These functions mean that some libraries will need considerably more computer power and new staff with technical computing skills to add to the expertise of librarians. Additional costs are to be expected in information processing. In a review of the field of hospital information management, for example, Grams and co-workers forecast "continued growth in the data processing expenditures to the area of 6% to even 10% of the total annual budget of an institution."[37] This commitment of new resources to libraries is a necessary one. Vendors are intent on securing a market for their own files under proprietary searching software and not on optimizing the use of a competitor's data bases. Current search software, for example, is woefully difficult to use due to a lack of self-evident procedures in moving users between data bases easily and in providing feedback mechanisms to improve products. It will be up to entrepreneurial libraries and librarians to build tools that meet the information needs of health care professionals.

These are the first, admittedly primitive and necessary although not sufficient, steps toward the ultimate and distant goal of knowledge represented in a way that is susceptible to machine inference—that is, new knowledge acquisition, assimilation and manipulation similar to Wells's concept of a world brain.

A world brain requires a world language or at the least the ability to understand and translate all languages. A critical and fundamental task for applying research on medical informatics is to develop the logical models and structure necessary to create a unified medical language. The Unified Medical Language System (UMLS) envisioned by the NLM in its bold and visionary program is "a single classification structure to which all medical language can be mapped" ("Request for Proposal NLM-86-111/PSP," *Commerce Business Daily,* Apr 11, 1986, PSA-9066, p 2). The tasks to be accomplished under the UMLS program are multidimensional and complex. They include characterizing the language of different information sources (literature, clinical records, data banks and knowledge bases) and designing methods of linking, merging and integrating existing thesauruses and classification schemes. The array of skills and knowledge required to work in this domain includes medical sciences, medical informatics, information science, linguistics, artificial intelligence, decision making, medical terminology and thesaurus construction.

Libraries and librarians can contribute to this major undertaking in a number of ways. Librarians who specialize in information services are experts in retrieval languages. This expertise frequently requires an understanding of the system structure and a thorough knowledge of query languages, thesauruses and classification systems. In addition, a skilled reference librarian, like a physician, is a diagnostician—able to elicit the precise nature of the information needed and to select the proper source from dozens that will satisfy this need. Expert systems that can thread their way through a labyrinth of information sources to the answer need to be built by librarians. Finally, iterative testing and evaluation of these experimental applications requires an appropriate "laboratory."

The library that manages a system of data bases that is integrated into an institutional information system is an ideal laboratory.

When the distinctions between communication and publication are less obvious and the boundaries between medical data and medical knowledge blur, the functions of health sciences libraries may be to manage and deliver synthesized knowledge.

Summary

The focus of computer usage in medical libraries is shifting from controlling, processing and managing library records to managing and distributing bibliographic and full-text data-base information on premises through local networks. These telecommunications networks will facilitate the exchange of information from disparate sources in a continuous electronic mode. It will be possible for users at their desks to locate information from an array of geographically distributed data bases, to transfer it to their local and personal workstations, to reformat and manipulate it, to assimilate it into another intellectual form and to redistribute it as a new document, publication or data base. Working with those in the field of medical informatics, libraries will assist in the developing, testing and dispersing of new mechanisms for storing and processing knowledge.

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The Computer as a Tool for Learning

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Experimenters from the beginning recognized the advantages computers might offer in medical education. Several medical schools have gained experience in such programs in automated instruction. Television images and graphic display combined with computer control and user interaction are effective for teaching problem solving. The National Board of Medical Examiners has developed patient-case simulation for examining clinical skills, and the National Library of Medicine has experimented with combining media. Advances from the field of artificial intelligence and the availability of increasingly powerful microcomputers at lower cost will aid further development. Computers will likely affect existing educational methods, adding new capabilities to laboratory exercises, to self-assessment and to continuing education.

(Starkweather JA: The computer as a tool for learning, *In* Medical informatics [Special Issue]. West J Med 1986 Dec; 145:864-868)

Computers have improved remarkably in both availability and capability, and their use in medical education is increasing. Computer programs not only provide assistance for learning facts and their relationships, but they have become useful tools for the learning of decision making and problem solving. It is likely that computer-based educational methods will continue to evolve and play a significant role in the overall development of future medical education methods.

The Development of Educational Assistance

The application of computers to education has a history of more than 20 years. It was preceded by the promotion of simpler teaching machines.[1] In 1959 a computer was reported being used as a teaching machine, but it was considered to be economically unsound.[2] Work on the application of computers to teaching continued, nevertheless, in technologic companies such as IBM,[3] Bolt, Beranek and Newman[4] and Systems Development Corporation.[5] At the University of Illinois (Urbana, Ill), learning stations were developed that linked students or curriculum authors to a central computer. By 1967 a survey listed 240 publications concerning computer-assisted instruction that had appeared between 1959 and 1967 and 20 centers in the United States where digital computers were dedicated for instructional systems.[6]

In the late 1960s, it was possible to place a student in communication with a large-scale computer for about the cost of using an individual tutor. It was imagined that costs would decrease, and there was considerable optimism in the business world that prompted a number of companies with computer facilities to join with publishing houses to develop computer-based materials. An example of this optimism was reflected in the August 1, 1968, issue of *Forbes* magazine (vol 102, p 44) in which its reporter predicted that computer-assisted instruction would become big business, bigger than textiles, rubber or paper:

> But the sharpest rate of gain (in educational expenditures) is almost certainly going to be in spending for machines and programs to enable teachers to teach more effectively and efficiently. At present, total spending in this area is only about $2 billion a year, most of it in textbooks. That $2 billion could easily swell to $10 billion within the next six years, with old-fashioned textbooks getting a smaller and smaller proportion.

In writing about the application of computers to medical education at about that time, I emphasized a need to teach clinical skills as well as necessary facts.[7] I was not alone in the belief that computers could provide practice in the skills of inquiry and problem solving. Others wrote of the need to give students practice in these skills and how computers could provide the means: they had the capacity to analyze and respond to relatively unconstrained input from a student; they gave rapid access to extensive information storage and retrieval, and they could give potentially unlimited competence in the field of instruction through access to the collected insight, experience and creativity of a large number of teachers.

The reputation of computer-assisted instruction, however, suffered ill effects from overpromotion similar to that which had occurred with programmed instruction using booklets, multiple-choice filmstrips, branching books and so forth. The former principal of a school where many new methods were tried wrote that "programmed learning has

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been oversold, overrated, overpriced and underproductive."[8] The materials were promoted long before carefully developed programs were designed to match the needs of particular students. Improvements in computer capability and reductions in cost have occurred much more rapidly than programming systems developed for education. The potential for computer use is perhaps more evident than ever, but applications that involve changes in long-established educational methods are slow to occur.

A good case can be made for the belief that instructional objectives should be stated not only in terms of information to be learned, but also in terms of observable behavior that can be expected from a student at the completion of a sequence of study. During the course of learning, students should be in a position to practice the behavior they are trying to master. Even though this seems to be a platitude, an example of contrasting approaches would be medical students who are asked to give a list of signs and symptoms associated with a disease rather than getting practice in attempting to solve a diagnostic problem on the basis of presented symptoms. Interactive instruction can allow students to practice behavior that is closer to their eventual goal.

Applying the Computer to Medical Education

Using a computer as an aid to learning holds a special appeal to those who have experimented with computers and who have also been involved in the education of physicians and other health care professionals. For example, a special interest group for health care educators was formed in the early years within the Association for the Development of Computer-based Instructional Systems and it has continued to be an active element. The potential seemed clear—that it would be possible to create problem situations for medical students that would be realistic clinical experiences. Such clinical exercises could pose diagnostic problems and confront students with the necessity to communicate in an interview situation, and the exercises could be reliably repeated for more than one student. The report, "Physicians for the 21st Century,"[9] commonly referred to as the GPEP report (for General Professional Education of the Physician), was a recent reiteration of earlier statements made by others along the same lines. It described the proliferation of factual knowledge within each specialty discipline and how this leads to rote learning and a lack of necessary integration and synthesis. It urged medical school faculties to reduce the dependency on lectures as the principal method of teaching and to increase activities that provide students with more opportunities for independent learning and for problem solving.

There is, nevertheless, a general resistance to change from the traditional methods by medical school faculty members. Interacting with a computer and self-pacing have not been clearly shown to be more effective than the usual teaching methods in terms of student performance. Faculty are also often reluctant to use programs developed at other schools. The result is the occasional, scattered use of computer-based materials introduced as optional adjuncts to existing courses.

Uses for Automated Instruction

Because introducing computer-based methods is likely to be incremental, the following may be some appropriate criteria for identifying situations in which automated instruction will be best suited. First, automated instruction is particularly useful where it is necessary to teach complex and sequential decision-making processes. Second, it is particularly useful where discriminations among complex stimuli must be learned. Third, it is useful where there is a large proportion of people who need to acquire information at times when they cannot be taught as part of a large group of learners.

Many aspects of medical education seem to have these characteristics. Not only do medical students require instruction at irregular times related to specialized schedules in various services and departments, but students, interns, residents and other staff are faced with rapidly growing knowledge and changing techniques that they must master. Computer-based methods can provide experiences with cases not often seen or with procedures that would be dangerous if actual patients were used. Other advantages are that students can control access to instruction to meet their own needs and pace, the learning can be private without risk to a student's self-esteem and realistic simulations can create an engrossing context in which learning is both enjoyable and motivating.

In spite of the expected benefits of computer-based learning and its general acceptance by students, studies of student achievements have not shown an advantage. This may be due to the difficulty of measuring the effectiveness of teaching and comparing teaching methods, or it may be due to the primitive nature of person-computer communication that has so far been available. Many computer-based curriculum materials produced to date can be characterized as programmed instruction that could as easily be presented in the form of a low-cost book. Because of the additional time and effort required to convert such sequences into computer programs, such programs are not cost-effective.

There are now new possibilities that use the increasing graphic capability of computers and their interaction with other media. Until recently, the application of various technologies to instructional activity has proceeded almost entirely along separate lines described by the names of the separate audiovisual media—movies, slides, books, programmed instructional material and television. These have been used most often by those who specialize in one or another of these media. We are now seeing some integrated combinations of television and computers, however, with the computer providing users with adaptive effectiveness.

Major Existing Projects

The PLATO System

One of the largest organized collections of computer-based educational programs is the PLATO system, begun more than 20 years ago at the University of Illinois and later available from Control Data Corporation.[10] It was from the beginning an ambitious project, one combining high-resolution graphics on a specially designed plasma display terminal and the projection of images on the same display from a random-access microfiche projector. Terminals connect to a centrally located large computer by leased telephone lines. There is now also a version that can operate many of the same programs on a free-standing microcomputer. The programs are written in an authoring language called TUTOR that, like other specialized computer languages such as MUMPS and PILOT, simplifies the process of developing lessons. The PLATO system grew to contain lessons for many subjects at

all levels of education. More than 400 lessons have been developed at different medical schools and collected in the system. They differ widely in approach, some operating in a testing mode, some providing tutorial exercises and drill of factual information and some running simulations that model a portion of the real world.

Ohio State University College of Medicine's System

Another large project that has provided services to medical schools is a library of instructional programs and related data bases developed at Ohio State University College of Medicine (Columbus, Ohio).[11] This project provides on-line access to computer-assisted instruction in most areas of health professions study and is probably the largest single collection of such coursework. It supports users from other medical centers in all parts of the country by the Health Education Network. This network, which developed as an experiment in shared computer-assisted instruction with support of the Lister Hill National Center for Biomedical Communications of the National Library of Medicine, has now operated on a commercial basis for more than ten years.

The medical school at Ohio State University has been an innovator in experimenting with independent study using computer-based materials that parallels the normal course of study. The curriculum covers introductory physiology, biochemistry, pathophysiology and therapeutics using modules that contain learning objectives, reading assignments, small group laboratory and conference sessions and computer-based testing. Volunteer groups of students have used these materials, and their progress compares favorably with classmates taking the traditional curriculum.

Computer-Aided Simulations of the Clinical Encounter

One of the most advanced portions of the aids to independent study available from Ohio State University are Computer-Aided Simulations of the Clinical Encounter (CASE). These originated at the University of Illinois College of Medicine (Chicago)[12] and were later moved to Ohio and the Health Education Network. A user assumes the role of physician and makes free-text inquiries of the simulated patient via a keyboard to develop diagnosis and management of the case.

Simulation Programs at Massachusetts General Hospital

Simulation of a somewhat different sort is shown in an extensive series of clinical management simulations at Massachusetts General Hospital (Boston).[13] Some of the simulations are of a physiologic system or process, such as electrolyte balance and its reactions to therapy. Some are diagnostic problems to be solved in which the simulation is a matrix of probabilities that medical findings such as history, physical examination information and laboratory results are associated with specific diagnoses. In other simulation exercises, the condition of an imagined patient changes in response to decisions of the student. These simulations, written in the MUMPS programming language, have been available to other medical centers by dial networks. Some of them have now been adapted for operation on microcomputers and are available for purchase from a commercial publisher. Currently available topics in this format are managing hypertensive emergencies, digitalis therapy, the treatment of arrhythmias, arterial blood gas measurement and cardiopulmonary resuscitation training.

Computer-Based Examination

The National Board of Medical Examiners, working with the American Board of Internal Medicine, has developed a computer-based examination called CBX that is a complex patient-case simulation requiring diagnosis and case management. It is an examining system that models reactions to drugs, interventions by the physician being tested, the passage of time and the constantly changing interactions between these variables. Pictorial slides or microfiche accompany the text information.

Useful learning materials can now be produced using videodisk technology without a separate computer. This is possible because a videodisk player contains a microprocessor that can control the choice of visual display. It responds to control sequences recorded on one of the two available audiotape tracks and in reaction to a user's responses with a keypad. Examples are videodisks on the management of trauma and neurologic disorders, produced at the University of Washington School of Medicine (Seattle), and a tutorial on nosocomial infections such as bacteremia[14] and surgical infections,[15] distributed by Miles Pharmaceuticals.

TIME

Adding a microcomputer along with videodisk images and sound allows more complex interactions and more realistic simulations. The same videodisk can be used in an instruetional or testing mode with a change in the controlling computer program. An experimental system called Technological Innovations in Medical Education (TIME) has been developed at the Lister Hill Center of the National Library of Medicine.[16] A student user reacts to dramatic portrayals of a patient's medical and social conditions and is expected to do so without prompting. The microcomputer is trained to recognize a user's voice with a selected vocabulary so that a student makes uncued, verbal interventions in the course of managing a case. Other experimenters have developed similar portrayals of medical problems and emergencies requiring decisions that must be made in real time as one interacts with the program. Such simulations can be highly realistic and motivating. While there is yet no comprehensive catalogue of instructional software and very little interchange of materials from one institution to another, in a recent summary an attempt was made to cover all simulation programs that provide practice in clinical case management.[17] The result of a national survey, this catalogue lists nearly 100 interactive programs that deal with strategies of patient care. It provides information about developers and distributors, system requirements for operation and suggested audiences.

Other Systems

From experiments in artificial intelligence, systems have begun to be developed with expert knowledge in specific fields. They operate as consultants on diagnostic and case management problems. With minor modification of use, they have potential as self-directed learning aids. The Quick Index to Caduceus Knowledge (QUICK) is an application program built on the INTERNIST-1 knowledge base (now called Caduceus) developed at the University of Pittsburgh School of Medicine (Pittsburgh).[18]* It is an electronic textbook of medi-

*See "The INTERNIST-1/QUICK MEDICAL REFERENCE Project—Status Report" by R.A. Miller, MD, M.A. McNeil, MD, Sue M. Challinor, MD, et al, elsewhere in this issue.

cine that allows a physician to get information directly from the Caduceus knowledge base, and it can be used as a diagnostic aid or as a teaching tool. The user can obtain a profile of a disease or a differential diagnosis of presented findings. NEOMYCIN is an application of an existing expert system for teaching purposes, one that teaches how to solve diagnostic problems of infectious meningitis.[19] HEARTLAB is a program being developed at Harvard Medical School that makes use of both graphic display and sound-generating capabilities of the Apple Macintosh computer to allow students to learn variants of heart sounds in an exploratory fashion and then to test their diagnostic ability (B.P. Bergeron, MD, written communication, April 1986).

The Directions of Further Development

There will probably be a useful place for drill and practice programs and those that test for the retention of necessary facts. The direction of greater improvement, however, is in more programs that assist with decision making and problem solving and help the learning of such skills. There are a number of changes in both hardware and software technology that will make such improvement possible with what will very likely be an increasing rate of change.

Hardware capabilities continue to increase rapidly, and they already offer more possibilities for information display, the collection of responses, record keeping and adaptation to a user than have been yet applied to instructional programs. Lowered equipment cost is allowing students to have access to convenient and powerful workstations. The storage of large amounts of information is rapidly dropping in cost, and the display of information is becoming increasingly effective with higher resolution graphics and the use of color. Computer control of images from videodisks is likely to become less expensive and easier to produce. Many students will have gained experience with their personal computers, and they will be more prepared to take advantage of computer assistance. Awareness of computer possibilities is also likely to increase for physicians in practice. Instructional programs for continuing education will become available to operate on local equipment in common use. It is already clear that advantages in availability, speed, reliability, lower cost and the avoidance of data communication difficulties have prompted the migration of many programs to microcomputers as these computers have become more capable.

There is a need to produce educational software that is general enough that it can operate with different specific equipment. This seems necessary both because the hardware keeps changing and improving at a rapid rate and also because standardization to a particular configuration does not seem likely. As more students begin to have their own computers, there will be differences between student equipment and school equipment and differences in the school equipment used in different departments. Software representing a large investment, such as complex models simulating clinical conditions or large knowledge bases, needs to remain usable even as there are changes in the technology with which they are stored and accessed.

Improving Existing Methods

Perhaps it would be helpful to think of computer assistance to learning in the context of how computers may improve existing educational elements and methods. For example, computer assistance should be applied to developing better tutors, better textbooks, better laboratory exercises and even better lectures. In addition, computers should improve information access for students, both from library collections and from instructors. Electronic mail between students and between students and instructors should become an available resource.

A Tutoring Computer System

Computer systems should interact using programs that act less like a lecturer and more like a responsive tutor. As computer programs develop more inference capability in a particular problem area, we should see programs that leave the initiative to students, programs that are able to recognize common student errors and ones that can provide advice when requested. Rather than simply present information, ask questions and then branch appropriately to new information, an expert tutor program will place a student in the position of primary agent, but be ready with assistance. We foresee that it will be difficult to assess the ability of such a tutor because as programs become more complex, the problem of assessment will become one of a similar difficulty to that of evaluating human teachers.

Textbook Adjuncts

Computer systems can improve the representation of concepts by providing adjuncts to textbooks such as animated drawings and graphic displays that can be manipulated by a student. Animation can help students to visualize a sequence of events in a time-related variable. Manipulating an image, such as rotating or expanding details, will go far beyond what can be shown with a defined set of pictures in the usual text. Such materials can be catalogued and described for use in a variety of instructional programs.

Simulating Laboratory Exercises

Better laboratory exercises should result from the involvement of computers. It will be possible to simulate the elements of a laboratory so that students can carry out experiments by interacting with a computer. Such a virtual laboratory can act as a precursor and an introduction to actual laboratories, with useful prompting of students to recognize important indices and to explore their variation and effects. Some programs will provide data on the basis of an underlying model and let a student compare them with predictions from alternative theories, or compare them with data gathered from larger samples. Some will operate more in direct simulation of a model and encourage a student to change some variables and observe the effects on others.

We are likely to continue to have lectures, but they can be improved with computer assistance. Just as graphics produced by a computer are an extension of what is found in textbooks, new technology can produce large-screen graphic displays with high resolution that can go far beyond what a lecturer can produce with a blackboard. It seems feasible to expect that displays generated during a classroom presentation would be available at workstations for further use outside of class at a student's own pace of learning.

Self-Assessment and Continuing Education

In general, a steadily improving interaction between computers and students will likely increase the use of computer-

based tools for medical learning. New programs will probably emphasize simulations that can assist in the learning of decision making and problem solving. In a recent review of medical information science in which computer-based education was considered,[20] the conclusion was reached that the primary implications of developments in computer-based medical education relate to continuing education and testing. Programs that can operate on a physician's own computer will have the advantages of self-directed learning and self-assessment whenever time permits. For this reason, computer-based access to self-assessment as well as instructional material has particular usefulness for continuing education. Areas of weakness or gaps in knowledge are likely to be individually different, and professionals in mid-career may be much more comfortable in exploring their own competence in private than in public.

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Learning Resources for Medical Computing

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For medical professionals to acquire computer literacy can be an arduous task. Resources for learning medical computing fall into four major categories: learning technical microcomputer use, computerizing an office practice, tracking patient care experience and integrating medical information systems. Both microcomputer use and tracking patient care experience are technical skills similar to learning any medical procedure with which physicians are already familiar. These skills can be acquired by consulting general, commercial resources such as computer stores, popular computer magazines or software manuals. Computerizing an office practice involves diagnosing office information problems by thoroughly analyzing how data flow during outpatient care. Medical information system design and management is a cognitive specialty in which principles of computer science and medical information management are applied to patient care experience.

(Jelovsek FR: Learning resources for medical computing, *In* Medical informatics [Special Issue]. West J Med 1986 Dec; 145:869-871)

Physicians frequently ask, "Where can I learn about medical computing?" What they usually mean by this question could be one or more of the following more specific questions:

1. Where can I learn to use a personal computer?
2. What is the best way to computerize my office practice?
3. How can I keep track of my patient care experience?
4. Where can I learn about the fine points of possible medical applications that might be used with the medical information system I work with?

The first question implies wanting to learn a technical skill that is similar to many of the manual skills learned by medical students, such as doing a lumbar puncture, a thoracentesis or a specialty physical examination. The second question implies a desire to solve a not-yet-defined problem. Often a physician has an office manager who is instructed to find an office computer system and implement it to improve cash flow and data retrieval in the practice. The third question presupposes a knowledge of the technical aspects of operating a personal computer and addresses a common desire of many physicians to keep detailed files on specific patient types in their practices. The purpose of this computerization could be to write about their experience or to discover some relationship that will contribute to new medical knowledge about a disease. The fourth question indicates a desire to learn the principles of medical informatics to more effectively computerize and integrate a medical information system according to a physician's professional needs.

The following discussion of learning resources for medical computing has been categorized according to the tenor of the questions asked above.

Learning Technical Microcomputer Use

Many local colleges, vocational schools and, sometimes, dedicated commercial educational centers offer introductory courses in microcomputer use. In a classroom students receive hands-on experience using a particular brand of microcomputer. These courses are places to begin but one should beware of courses that try to teach a programming language using a lecture setting with access to terminals connected to the school's minicomputer. Computer programming is not the best beginning for students who want to learn how to operate and run a specific computer application. Before these introductory "hands-on" courses became available and even to a large extent now, most technical computer skills have been self-learned after a microcomputer has been purchased for home use. Some have been fortunate enough to learn to use a microcomputer in a business or professional setting, but the learning curve for most learners does not rapidly ascend until they have a home unit to practice on. In a sense, this is an expensive way to learn computer use, but, in another sense, it is the only way that consistently works. Attending local computer store courses on the "disk operating system" (DOS) or a specific word processor, data base or spread sheet is the next step, especially if self-learning is thwarted by poorly written manuals. After buying a software applications package, a person can often sit down with the manual and learn how to

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operate the program, but an introductory course in that software can save hours of frustration.

Last, general magazines (see Appendix, numbers 1 and 2) and those that are specific to the personal computer to which a person has access (numbers 3 to 8) are a major information source. Reading articles and looking at the ads are popular ways of continuing to learn, and this is especially the case in the personal computer fields. The cost of two to three magazine subscriptions is well worth the expense, even if there is time only to skim the issues periodically.

In general, it takes about two years (on an after-hours basis) after having access to a microcomputer to become accomplished in the technical "how-to-do-it" aspects of computing. During that time a software applications program can be used productively, but it takes most people that long to feel comfortable with adding new hardware components to their computer, obtaining the innumerable little software subroutines necessary to make life easier, adjusting start and stop bits and the baud rate for telecommunications and having the confidence to explore new applications on their own.

As a physician becomes more proficient in using a microcomputer, he or she may decide to write computer programs either for personal use or as development for resale to other users in a particular specialty. There are more advanced magazines available for those who get the "hacker" spirit (Appendix, numbers 9 and 10).

Computerizing an Office Practice

Computerizing an office practice is not itself an educational goal. One physician may want to improve cash flow, whereas another may just want to have better patient data at hand. Some physicians are more interested in computerizing the medical record aspects of their office practices and would prefer to leave accounting to a current manual, batch or service system. Data gathered during a patient visit, such as diagnoses, procedures or therapies, have both medical and financial meaning. There is no point in having a patient's bill give one diagnosis when the physician's medical notes show another, and yet medical data are collected that are unnecessary for the accounts-receivable system.

Alternatively, there is much financial and administrative information that physicians do not want cluttering their medical notes. Information flow in an ambulatory medical setting is much more complicated than most physicians realize. They are aware of their medical data requirements but often do not fully understand their own practice's financial and administrative needs.

If a physician's practice does not currently have an office computer system, I recommend that one or more physicians in a practice become familiar with personal computers before committing to any office software. By spending a year or even two in learning what can and cannot be done with personal computers, physicians will save several thousand dollars or more in computerizing their office system, just by being familiar with computer terminology and with what are reasonable expectations of performance for office software (Appendix, numbers 11 and 12). The next step is to do a thorough analysis of data gathering and information flow in the medical practice (Appendix, number 13). There are usually at least 25 different documents on which a patient's name and medical record number may be written during a single patient visit. Physicians are usually only familiar with a few of the documents that they personally write on. Receptionists, insurance clerks, nurses and laboratory aides, however, can point out other documents that must be completed during a patient visit. After a thorough assessment of all current data forms is done and a list of current and desired reports is made, it becomes obvious how complex the logistics of data flow in a medical practice really are. Computer systems have been developed to handle all this information flow but they are usually minicomputer based and expensive (Appendix, number 14). If a physician buys a personal computer with one or two terminals and expects it to totally computerize his or her patient care data, a major disappointment awaits both physician and office staff. It is usually better to grow into the data-processing requirements by starting with smaller aspects of the the total patient flow and then determining where the major payoff to computerization will occur. (Appendix, numbers 15 and 16).

Tracking Patient Care Experience

Physicians-in-training learn to collect patient historical and physical data in detail, to organize the medical record along traditional formats and add to the initial assessment a time series of patient encounters focused on a specific medical problem. Personal computers and commercially available data-base managing systems can be used to record this patient care experience for defined medical categories. It is difficult to process the entire medical record for any one of 10,000 possible patient problems on a personal computer, but if physicians want to follow all of their patients who have diabetes mellitus or hypertension, for example, this can and should be done.

To learn this, data-base managing software should be selected that runs on an available microcomputer. There may be courses offered at a local computer store for the more popular selling data-base managing systems, but, for the most part, people learn by sitting down with a computer manual and creating patient files by trial and error. Creating a patient data base is an iterative function in which the data elements and their relationships are defined, sample patient data are recorded, the data elements and their relationships are revised and then actual patient data are recorded. There are usually from three to six different attempts at defining data-base content until a "final" (only for the next six months) format is settled on for regular data entry. Physicians should look for commercially available software packages that:

- Can easily calculate the number of days between two dates.
- Store their records as variable-length free text. (For a last name of "Smith," only 5 characters of storage are allocated instead of 18 characters that users may have defined as the maximum length for a last name.)
- Uses a data dictionary or relational records to accommodate list variables such as diagnoses, procedures, medications, providers and the like.

The above features tend to characterize medical data bases versus features for business data bases. Setting up a simple patient data base is so fundamental to medicine that it should be taught in medical school. Not only is it helpful to practicing physicians, but residents and fellows will find this skill indispensable. Seldom is hiring a programmer to computerize one's records or ordering a computer-literate subordinate to

set up one's programs successful. I used to think these were reasonable alternatives but have learned that information systems should be designed by those people who are the users of the information. In the case of patient care experience, that user is a physician.

Integrating a Medical Information System

All physicians will eventually learn to use a computer as a tool to make the daily practice of medicine more efficient. They may use one for patient case records, as aids to medical decision making or for telecomputing to "dial-up" medical data bases. Only a small subset of those physicians, however, will delve into the cognitive basis of medical informatics (Appendix, numbers 17 and 18). Most physicians will not feel the need to keep aware of informatics development in specialty fields other than their own; to attend scientific presentations on research and development in medical informatics, or to worry about generic problems such as patient identification and record linkage in medicine, the influence of data-recording techniques on error rates in medical data, the advantages and disadvantages of different medical coding and nomenclature systems or the strengths and weaknesses of mathematical-based decision support programs versus rule-based expert systems.*

Those who work with medical information systems on a daily basis or who serve as educators in medical schools will find support in professional associations (Appendix, numbers 19, 20 and 21) and annual symposia and conferences (numbers 22 and 23) that will help keep them up-to-date on current developments. There are peer-reviewed scientific journals that cover this field (numbers 24, 25 and 26) and educational journals (number 27) and newsletters (number 28) that one can use as information resources. Readers who think they might be interested in this degree of informatics involvement should attend one of the fall symposia or spring congresses that are conducted for persons in the medical profession. Following that, a person may want to join a professional organization that includes a subscription to its learning journals and provides forums for sharing problems with others who have similar interests (number 19). For those who remain in the field for several years or obtain advanced degrees in medical informatics, it is possible to look forward to a collegial fellowship of other professionals in medical informatics (number 21) who help define and support this newly emerging medical specialty field.

*See "Medical Expert Systems—Knowledge Tools for Physicians" by E. H. Shortliffe, MD, elsewhere in this issue.

APPENDIX

Resources for Further Information*

Popular Magazines—News and Introductory

1. Byte, Subscription Dept, PO Box 597, Martinsville, NJ 08836
2. InfoWorld, PO Box 1018, Southeastern, PA 19398
3. PC Magazine [IBM compatibles], PO Box 2445, Boulder, CO 80322
4. PC Week [IBM compatibles], Circulation Dept, One Park Ave, 4th Flr, New York, NY 10016
5. PC World [IBM compatibles], Subscription Dept, PO Box 6700, Bergenfield, NJ 07621
6. Macworld (Macintosh), Subscription Dept, PO Box 51666, Boulder, CO 80321
7. A+ [Apple, Macintosh], PO Box 40317, Philadelphia, PA 19106
8. Incider [Apple], CW Communications/Peterborough, PO Box 911, Farmingdale, NY 11737

Magazines—Technical

9. PC Tech Journal, PO Box 2968, Boulder, CO 80321
10. Dr Dobb's Software Journal, 2464 Embarcadero Way, Palo Alto, CA 94303

Books—Office Practice

11. Oberst BB, Reid RA (Eds): Computer Applications to Private Office Practice. New York, Springer-Verlag, 1984
12. Neiburger EJ: Computers for Professional Practice. Waukegan, Ill, Andent, Inc, 1984 [1000 North Ave, Waukegan, IL 60085]
13. Jelovsek FR: Doctor's Office Computer Prep Kit. New York, Springer-Verlag, 1985

Books—Overview Medical Informatics

14. Blum BI (Ed): Computers and Medicine: Information Systems for Patient Care. New York, Springer-Verlag, 1984
15. Norris DE, Skilbeck CE, Hayward AE, et al: Microcomputers in Clinical Practice. New York, John Wiley & Sons, 1985
16. Javitt J (Ed): Computers in Medicine: Applications and Possibilities. Philadelphia, WB Saunders, 1986
17. Covvey HD, Craven NH, McAlister NH: Concepts and Issues in Health Care Computing, Vol 1. St Louis, CV Mosby, 1985
18. Blois MS: Information and Medicine: The Nature of Medical Descriptions. Berkeley, Calif, University of California Press, 1984

Organizations and Associations

19. American Association for Medical Systems and Informatics (AAMSI), 1101 Connecticut Ave NW, Washington, DC 20036
20. Society for Medical Decision Making, Gamble and Associates, PO Box 447, West Lebanon, NH 03784
21. American College of Medical Informatics, c/o Thomas E. Piemme, MD, Secretary, George Washington University, 2300 K St NW, Washington, DC 20037

Scientific Meetings

22. Symposium for Computer Applications in Medicine (November), The George Washington University Medical Center, Office of Continuing Education, 2300 K St NW, Washington, DC 20037
23. AAMSI Spring Congress (May)

Peer-Reviewed Scientific Journals

24. Computers and Biomedical Research, Academic Press, 6277 Sea Harbor Dr, Orlando, FL 32887
25. Journal of Medical Systems, Plenum Publishing Corp, 233 Spring St, New York, NY 10013
26. Methods of Information in Medicine, F.K. Schattauer Verlag GmbH, 7000 Stuttgart 1, Postfach 2945, Lenzhalde 3, Germany

Educational Journals

27. MD Computing, Springer-Verlag New York Inc., Service Center Secaucus, 44 Hartz Way, Secaucus, NJ 07094

Newsletters—General Medical

28. Computers in Medicine, PO Box 36, Glencoe, IL 60022

*This is not intended to be an exhaustive list but rather provides guidelines for not wasting one's money.

The Computer and the Future of Continuing Medical Education

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Traditional continuing medical education—general reading, attending courses and conferences and having discussions with colleagues—helps physicians review fundamental concepts and learn new developments in medicine. This type of continuing education is well established and will not change dramatically. Beyond this, physicians learn from specific problems that arise in practice. A computer can enhance practice-related continuing medical education by providing information when a physician is developing diagnostic and therapeutic plans. Computer mail and telephone voice mail improve communication among physicians. Computers, by storing practice data, enable physicians to study their practices and profit from experience. Hospitals, specialty societies and medical schools should investigate using computers to help physicians profit maximally from experience.

(Manning PR: The computer and the future of continuing medical education, *In* Medical informatics [Special Issue]. West J Med 1986 Dec; 145:872-873)

Traditional continuing medical education is designed to help physicians review fundamental concepts and learn new developments in medicine. The major methods of such instruction—courses, conferences, general reading and informal discussions with colleagues—have remained constant for the past 50 years.

Beyond formal continuing education, physicians need to address specific problems arising in their practice. The usual methods for addressing these problems are reading textbooks and medical journals and through informal and formal consultations with colleagues. In the United States, undergraduate clinical education has traditionally been based, insofar as possible, on actual problems that occur in patient care. Osler, a strong believer in this approach, said, "The student begins with the patient, continues with the patient, and ends his studies with the patient, using books and lectures as tools as means to an end."[1] Oliver Wendell Holmes concurred:

> The most essential part of a student's instruction is obtained . . . not in the lecture-room, but at the bedside. Nothing seen there is lost; the rhythms of disease are learned by frequent repetition; its unforeseen occurrences stamp themselves indelibly in the memory.[2]

The development of experience-based continuing education can lead to a real breakthrough in continuing medical education. I am convinced that medical care will be improved when more attention is focused on techniques that permit physicians to learn systematically from actual events in practice, with less emphasis on formal conferences and courses.[3] Many outstanding physicians have developed personal methods for doing this, such as keeping notes on instructive cases and organizing a personal reprint file for immediate access to valuable journal articles. Manual approaches that well-motivated physicians use are often time-consuming and cumbersome, but computers will undoubtedly make practice-based continuing medical education more efficient.

Providing Information When and Where It Is Needed

Many library services are already available to physicians who have microcomputers. MEDLINE, an on-line computer version of the *Index Medicus*—the index of medical literature published by the National Library of Medicine—includes more access points and more speedily identifies relevant articles than its printed counterpart. The National Library of Medicine produces several other computerized indexes, including TOXLINE, CHEMLINE, CANCERLIT and AVLINE. Three commercial vendors—Bibliographic Retrieval Services, Lockheed Dialog and Systems Development Corporation—provide additional data bases covering physical and social sciences, humanities and business. Dialog offers *Excerpta Medica* with good coverage of clinical medicine and an emphasis on drugs.

These electronic services give physicians access to titles

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and abstracts of journal articles from which they can determine their applicability to patient problems. As accessibility of the medical literature by computer improves, we anticipate that all physicians will be able to call forth pertinent journal articles readily on their personal computers.

Many information services also provide abstracts of current medical developments and events reported in medical journals. It is likely that medical societies, and perhaps medical schools, will provide members with daily summaries of interesting medical articles by computer mail.

Jeghers has been a major force in influencing medical students and physicians to keep personal reprint files of articles pertinent to their practice.[4] These files become unique collections for individual physicians. By simplifying cross-indexing and storing journal abstracts, a computer can make personal reprint files more useful than ever. In addition, a computer can store abstracts of instructive cases, providing a useful resource for physicians to use to profit from their experiences.

Aiding Communication Among Physicians

A most useful method of continuing education is informal communication among physicians, which often takes place at nurses' stations, in hospital hallways and parking lots, during lunch or through chance encounters. Physicians may hesitate to call a colleague during practice hours for fear of interrupting a patient visit, or they may be unable to reach another physician because he or she is in surgery, on hospital rounds or traveling between office and hospital. Computer mail permits more efficient communication among physicians. At their convenience, physicians can make inquiries that will be stored in a computer, to be answered at the convenience of the receiving physician. This system avoids what some people call "telephone-tag" and eliminates chance encounters.

Voice mail, which uses a touch-tone telephone, makes communication among colleagues even more efficient. A physician simply dials an 800 number, directs a communication to a particular colleague by a code number and records a message that is stored in the computer in digital form, to be called forth by the second physician at his or her convenience. Voice mail requires no additional equipment, and physicians may receive and send messages from any touch-tone telephone in the United States.

Studying One's Practice

Osler, in emphasizing the importance of learning from patients, suggested that physicians

> Begin early to make a three-fold category—clear cases, doubtful cases, mistakes. And learn to play the game fair, no self-deception, no shrinking from the truth; mercy and consideration for the other man, but none for yourself, upon whom you have to keep an incessant watch.[5]

Physicians in the US typically file their office records by name and perhaps a registration number. Few physicians index their patient records by clinical problem or diagnosis and therefore cannot systematically review their diagnostic and therapeutic plans on specific conditions. Thus, they lose the opportunity of learning from their composite experience or of comparing their diagnostic and therapeutic plans on particular problems with those of colleagues. Computers, again, simplify the cross-indexing of charts by patient's name and condition. Studies indicate that physicians often do not know their case mix or the frequency with which they prescribe certain drugs, order certain laboratory studies or carry out certain procedures.[6] Computers can facilitate a practice profile and thus permit physicians to analyze and better understand their practices for more effective continuing education. Although physicians may fear comparing their practice profiles with those of colleagues with similar practices, the comparison would be useful for discussion and learning. Conceivably, specialty societies could offer individual continuing education based on a physician's practice profile.

Receiving Guidance

The opportunity to receive from a computer direct guidance on diagnosis and therapy will be discussed in more detail in another article in this series.* These guidance programs, currently experimental, will undoubtedly play a significant role in future diagnosis and treatment and will be powerful educational tools. Excellent programs in the differential diagnosis of cases of acute abdominal pain and of rheumatic diseases have already been developed. Miller, Pople and Myers have developed the most inclusive diagnostic aid, INTERNIST, which now comprises more than 500 individual diseases and 3,550 manifestations.[6] Another such program, ONCOCIN, provides guidance in cancer chemotherapy.[7]

Computer-Assisted Instruction

A computer, when linked with a videodisc, can present information that includes still and motion pictures. With a videodisc it is possible to construct patient-management problem programs that permit physicians to answer specific questions and receive feedback on the accuracy of their answers. In fact, almost any type of simulation can be constructed with a computer and a videodisc. This type of education differs from the practice-linked continuing education that relates specifically to a physician's own practice.

Conclusions

If we are to achieve a major change in continuing medical education beyond the three traditional methods of conferences, reading and informal discussion with colleagues, computers offer the best opportunity by linking education to practice. Although hardware and software exist that permit implementing the approaches discussed here, it is clear that effective usage by physicians in office or hospital practice will require simplification and easier accessibility so that physicians may become comfortable with the techniques. Toward this end, hospitals, specialty societies and medical schools can help by conducting implementation experiments and emphasizing the need for simplicity in available software.

*See "The INTERNIST-1/Quick Medical Reference Project—Status Report" by Randolph A. Miller, MD; Melissa A. McNeil, MD, and Sue M. Challinor, MD, et al, elsewhere in this issue.

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In Memoriam

California Medical Association

BABCOCK, MYRON F., Burbank. Died May 29, 1986, aged 81. Dr Babcock was a member of the Los Angeles County Medical Association.

❦

BAUTISTA, MACARIO D., Stockton. Died Oct 1, 1986, aged 92. Graduate of College of Physicians and Surgeons, San Francisco, 1920. Licensed in California in 1920. Dr Bautista was a member of the San Joaquin County Medical Society.

❦

BEHRENS, MANFRED IVAN, Berkeley. Died Aug 6, 1986, aged 50. Graduate of New York University, 1962. Licensed in California in 1970. Dr Behrens was a member of the Alameda-Contra Costa Medical Association.

❦

BLUNDELL, CRAIG R., Escondido. Died Jul 28, 1986, aged 37. Graduate of University of Oregon School of Medicine, 1975. Licensed in California in 1976. Dr Blundell was a member of the San Diego County Medical Society.

❦

BOVILL, EDWIN G., San Francisco. Died Aug 29, 1986, aged 67. Graduate of University of Pennsylvania, 1943. Licensed in California in 1949. Dr Bovill was a member of the San Francisco Medical Society.

❦

BRAY, JAMES L., Los Angeles. Died Sep 8, 1986, aged 83. Graduate of Vanderbilt University, Nashville, Tennessee, 1931. Licensed in California in 1938. Dr Bray was a member of the Los Angeles County Medical Association.

❦

CHAPMAN, CARRIE ETHELYN, Laguna Hills. Died Sep 16, 1986, aged 85. Graduate of Tufts University School of Medicine, Boston, 1934. Licensed in California in 1952. Dr Chapman was a member of the Alameda-Contra Costa Medical Association.

❦

DARBY, JOHN B., Walnut Creek. Died May 29, 1986, aged 75. Dr Darby was a member of the Alameda-Contra Costa Medical Association.

❦

DE BERNARDI, DAVID JOHN, Anaheim. Died Jun 10, 1986, aged 36. Graduate of University of California, Irvine, California College of Medicine, 1976. Licensed in California in 1978. Dr De Bernardi was a member of the Orange County Medical Association.

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DE GRAZIO, JAMES V., San Gabriel. Died May 25, 1986, aged 62. Graduate of University of Southern California School of Medicine, Los Angeles, 1957. Licensed in California in 1958. Dr De Grazio was a member of the Los Angeles County Medical Association.

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GARDNER, KENNETH D., Sr, San Francisco. Died Oct 23, 1986, aged 85. Graduate of Stanford University, 1927. Licensed in California in 1927. Dr Gardner was a member of the San Francisco Medical Society.

HARRISON, RICHARD S., Pasadena. Died Feb 7, 1986, aged 79. Graduate of Oxford University, 1930. Licensed in California in 1940. Dr Harrison was a member of the Los Angeles County Medical Association.

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HILLYER, EDWIN A., San Diego. Died Apr 26, 1986, aged 73. Graduate of Stanford University School of Medicine, Stanford, California, 1942. Licensed in California in 1942. Dr Hillyer was a member of the San Diego County Medical Society.

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❦

LASK, SALVADORE A., Lancaster. Died Apr 26, 1986, aged 67. Graduate of University of Illinois College of Medicine, Chicago, 1943. Licensed in California in 1952. Dr Lask was a member of the Los Angeles County Medical Association.

❦

LUSK, ROBERT W., Clovis. Died Apr 2, 1986, aged 60. Graduate of Yale University School of Medicine, New Haven, Connecticut, 1951. Licensed in California in 1953. Dr Lusk was a member of the Fresno-Madera Medical Society.

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❦

NOYES, F. LE GRAND, Los Angeles. Died Apr 5, 1986, aged 86. Graduate of Jefferson Medical College, Philadelphia, 1925. Licensed in California in 1928. Dr Noyes was a member of the Los Angeles County Medical Association.

ODGERS, STEPHEN LAFAYETTE, Claremont. Died Mar 11, 1986, aged 76. Graduate of University of Kansas, Lawrence, 1937. Licensed in California in 1955. Dr Odgers was a member of the San Bernardino County Medical Society.

❦

PETERSEN, HAROLD E., San Fernando. Died Feb 27, 1986, aged 85. Graduate of Loma Linda University School of Medicine, 1925. Licensed in California in 1925. Dr Petersen was a member of the Los Angeles County Medical Association.

❦

PROCTOR, DAVID T., Pasadena. Died Mar 23, 1986, aged 87. Graduate of Rush Medical College, Chicago, 1925. Dr Proctor was a member of the Los Angeles County Medical Association.

❦

QUALIA, RENALDO R., Rosemead. Died May 12, 1986, aged 71. Graduate of Loma Linda University School of Medicine, 1944. Licensed in California in 1944. Dr Qualia was a member of the Los Angeles County Medical Association.

❦

RANEY, FRANK L., San Francisco. Died Feb 20, 1986, aged 62. Graduate of University of California, San Francisco, School of Medicine, 1947. Licensed in California in 1948. Dr Raney was a member of the San Francisco Medical Society.

❦

REED, PAUL H., Laguna Hills. Died May 12, 1986, aged 84. Graduate of Rush Medical College, Chicago, 1929. Licensed in California in 1936. Dr Reed was a member of the Los Angeles County Medical Association.

❦

ROKAW, STANLEY N., Downey. Died Apr 10, 1986, aged 64. Graduate of Washington University, St Louis, 1949. Licensed in California in 1955. Dr Rokaw was a member of the Los Angeles County Medical Association.

❦

ROWE, M. JOHN, Jr, Long Beach. Died Mar 5, 1986, aged 75. Graduate of University of Michigan Medical School, Ann Arbor, 1934. Licensed in California in 1934. Dr Rowe was a member of the Los Angeles County Medical Association.

❦

SHAPIRO, ABE OBBY, Los Angeles. Died Apr 3, 1986, aged 78. Graduate of Ohio State University College of Medicine, Columbus, 1932. Licensed in California in 1934. Dr Shapiro was a member of the Los Angeles County Medical Association.

❦

SIDERIUS, NORMAN J., San Diego. Died Feb 25, 1986, aged 57. Graduate of Boston University School of Medicine, Boston, 1956. Licensed in California in 1972. Dr Siderius was a member of the San Diego County Medical Society.

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❦

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❦

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❦

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❦

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❦

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Utah State Medical Association

CROWDER, ROBERT M., Salt Lake City. Died Oct 8, 1986, aged 77. Graduate of Northwestern University, Chicago. Dr Crowder was a member of the Salt Lake Medical Society.

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sembly of Southern California Hills, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

February 21—**Infertility Update IV.** Scripps Clinic and Research Foundation, La Jolla. Saturday. 6 hrs. Contact: Bonny Mower, Dept of Academic Affairs, Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

March 20-22—**Obstetrical Anesthesia—1987.** UCSF at Hotel Meridien, San Francisco. Friday-Sunday. Contact: UCSF.

March 25-28—**Gynecological Surgery With Emphasis on Vulvar and Vaginal Disease.** UCI at Hilton Riviera, Palm Springs. Wednesday-Saturday. 16.5 hrs. Contact: UCI.

April 2-4—**Fetal Diagnosis and Treatment.** UCSD. Thursday-Saturday. Contact: UCSD.

April 30-May 2—**12th Annual Symposium: Care of the Sick Newborn.** UCI. Thursday-Saturday. Contact: UCI.

May 6-10—**Annual Scientific Program and Postgraduate Courses.** Pacific Coast Fertility Society at Americana Canyon Hotel, Palm Springs. Wednesday-Sunday. 22 hrs. Contact: Pacific Coast Fertility Society, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

PATHOLOGY

January 17—**OB/GYN Pathology II.** USC at Pasadena Hilton Hotel. Saturday. 6.25 hrs. Fee: $105.

May 21-22—**Annual Meeting: Current Issues in Anatomic Pathology.** UCSF at San Francisco. Thursday-Friday. 12 hrs. Contact: UCSF.

PEDIATRICS

January 14—**26th Annual Parmelee Memorial Lecture and Practicing Pediatrician.** American Academy of Pediatrics and Los Angeles Pediatric Society at University Hilton Hotel, Los Angeles. Wednesday. Contact: LA Pediatric Society, PO Box 2022, Inglewood, CA 90305. (213) 757-1198.

January 19-21—**Pediatrics for the Primary Care Physician.** UCSD at Vacation Village Resort, San Diego. Monday-Wednesday. 16 hrs. Fee: $275. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 24-31—**Pediatric Emergencies.** Scripps Memorial Hospital, Encinitas at Kona Surf Resort, Hawaii. One week. 21 hrs. Fee: $375. Contact: Edith Bookstein/AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

January 25-28—**12th Annual Winter Ski and Study Program.** American Academy of Pediatrics at Caesars Tahoe Hotel, Lake Tahoe, Nevada. Sunday-Wednesday. 10 hrs. Fee: $250. Contact: AAP, Chptr 2, PO Box 2134, Inglewood 90305. (213) 757-1198.

January 30-February 1—**25th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Marriott Hotel. Friday-Sunday. 15 hrs. Fee: $175. Contact: Wayne Herbert, MD, Children's Hospital of Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

February 3-8—**16th Annual Pediatric Postgraduate Course: Pediatric Update 1987.** Schneider Children's Hospital of Long Island Jewish Medical Center, Rancho Las Palmas, Palm Springs. Tuesday-Sunday. Contact: Ann J. Boehme, Schneider Children's Hospital of Long Island Jewish Medical Center, New Hyde Park, NY 11042. (718) 470-8650.

February 5-7—**Current Concepts in Pediatric Medicine.** American Academy of Pediatrics at Holiday Inn Embarcadero, San Diego. Thursday-Saturday. 16 hrs. Fee: $330. Contact: Neal A. Baker, AAP, Division of Continuing Education, PO Box 927, Elk Grove Village, IL 60007. (800) 433-9016, or in Illinois (800) 421-0589.

February 12-13—**2nd Annual Pediatric Intesive Care Symposium.** UCI at Sheraton Newport Hotel, Newport Beach. Thursday-Friday. Contact: UCI.

February 16-18—**Pediatrics Update 1987.** Continuing Medical Education Associates at Hyatt Islandia Hotel, San Diego. Monday-Wednesday. 18 hrs. Fee: $275. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

March 5-7—**Advances in Pediatrics II.** American Academy of Pediatrics at Kauai, Hawaii. Thursday-Saturday. 16 hrs. Fee: $330. Contact: Neal A. Baker, Div of Continuing Education, AAP, PO Box 927, Elk Grove Village, IL 60007. (800) 433-9016, or in Illinois (800) 421-0589.

April 2-4—**20th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. 15 hrs. Contact: UCSF.

April 8—**Pediatrics: Genetics.** LLU. Wednesday. 4 hrs. Fee: $60. Contact: LLU.

PSYCHIATRY

December 28-January 3—**Psychiatry and the Practicing Physician—"New Year '87—Maui."** Hawaii Medical Association at Royal Lahaina Resort, Kaanapali Beach, Maui. Sunday-Saturday. 16.5 hrs.

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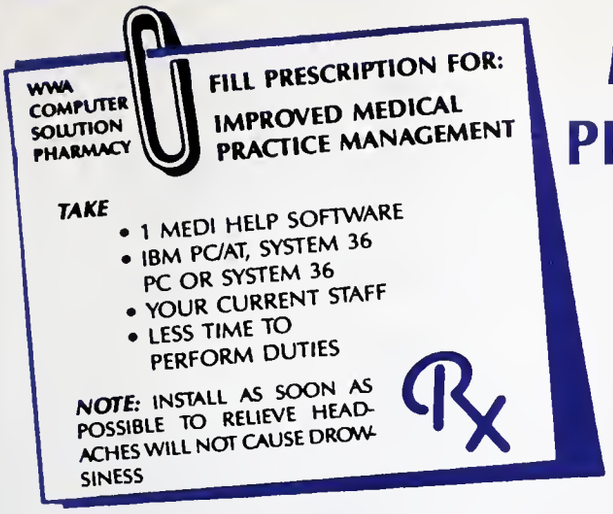

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Fee: $385. Contact: Joe Harrison, MD, Symposium Maui, Inc, PO Box 10185, Lahaina, HI 96761. (808) 879-8182.

January 25-30—**13th Annual Midwinter Program for Psychiatrists: Special Focus on Adolescent Psychiatry.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sunday-Friday. 25 hrs. Fee: $355-415. Contact: UCD.

March 28-29—**The Cutting Edge 1987: Difficult Treatment Problems With Borderline and Narcissistic Patients.** UCSD at Hotel Inter-Continental, San Diego. Saturday-Sunday. 13 hrs. Contact: UCSD.

April 10-11—**Mental Health in the Workplace.** UCSF at Cathedral Hill Hotel, San Francisco. Friday-Saturday. 11.5 hrs. Fee: $200. Contact: UCSF.

RADIOLOGY

January 9-13—**Advance Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Hotel, Laguna Niguel. Friday-Tuesday. 20 hrs. Contact: Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 12-16—**Neurodiagnostic Imaging: MRI.** UCSF at Hyatt Regency Hotel, San Francisco. Monday-Friday. Contact: UCSF.

January 13-16—**Chest Radiology—1987.** UCSD at Hotel Del Coronado, Coronado. Tuesday-Friday. 22 hrs. Contact: Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 22-24—**Practical Approach to Duplex Imaging.** UCSD at San Diego Hilton Hotel. Thursday-Saturday. Contact: UCSD.

January 30-February 1—**10th Annual Evoked Potential and Electrodiagnostic Workshop.** UCI. Friday-Sunday. 20 hrs. Contact: UCI.

January 30-February 1—**39th Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. 21 hrs. Fee: $350. Contact: Diane L. Johnson, Los Angeles Radiological Society, 5200 Century Blvd, Ste 920, Los Angeles 90045. (213) 642-0921.

February 2-6—**Radiology: Imaging and Intervention.** UCSD at Hotel Inter-Continental, San Diego.

Monday-Friday. Contact: R. Dawne Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

February 3-7—**13th Annual Midwinter Radiological Post Conference Seminar.** Los Angeles Radiological Society at Hyatt Regency, Kaanapali, Maui, Hawaii. Tuesday-Saturday. 18 hrs. Fee: $375. Contact: LARS-MWRC, PO BOX 91215, Los Angeles 90009-1215. (213) 642-0921.

February 11—**Interventional Radiology.** LLU at LLU. Wednesday. 4 hrs. Fee: $60. Contact: LLU.

February 21-28—**Radiology for Emergency and Primary Care Physicians.** Scripps Memorial Hospital, Encinitas at Royal Lahaina Resort, Maui, Hawaii. One week. 21 hrs. Fee: $375. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

March 2-5—**Neuroradiology Update.** UCSD at Hotel Del Coronado, Coronado. Monday-Thursday. 27.5 hrs. Contact: Mary J. Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

March 2-6—**The Annual Sierra Radiology Conference.** Sacramento Radiology Research and Education Foundation at Hyatt Lake Tahoe, Incline Village, Nevada. Monday-Friday. 20 hrs. Fee: $385. Contact: John P. McGahan, MD, SRREF, PO Box 19184, Sacramento 95819.

March 3-6—**Magnetic Resonance Imaging.** UCSD at Hotel Del Coronado, Coronado. Tuesday-Friday. 25 hrs. Contact: Mary J. Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

March 7-8—**Breast Imaging Update.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday. Contact: UCSF.

March 9-13—**30th Annual Diagnostic Radiology Postgraduate Course.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. Contact: UCSF.

March 14-15—**Contemporary Trends in Diagnostic Nuclear Medicine.** UCSF at Hyatt Regency Hotel, San Francisco. Saturday-Sunday. Contact: UCSF.

March 16-21—**Diagnostic Imaging—1987.** UCSF at Waiohai Hotel, Kauai, Hawaii. Monday-Saturday. Contact: UCSF.

April 9-11—**Thoracic Imaging—1987.** UCSF at Hyatt Regency, Monterey. Thursday-Saturday. Contact: UCSF.

April 10-12—**OB/GYN and Abdominal Sonography: Update 1987.** UCSF at Hyatt Regency on Union Square, San Francisco. Friday-Sunday. Contact: UCSF.

April 19-25—**7th Annual San Diego Residents' Radiology Review Course.** UCSD at Town and Country Hotel, San Diego. Sunday-Saturday. Contact: UCSD.

SPORTS MEDICINE

January 18-23—**Sports Medicine—1987.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sunday-Friday. Contact: UCD.

March 16-20—**Annual University of Hawaii: Sports Medicine.** Princess Kaiulani Hotel, Waikiki, Honolulu, Hawaii. Monday-Friday. 18 hrs. Fee: $300. Contact: Ms Joy Lewis, Box CEW-CCECS, 2530 Dole St, Honolulu, HI 96822. (808) 948-8244.

SURGERY

January 19-21—**American Society for Surgery of the Hand's 1st Winter Meeting.** Pacific Medical Center, San Francisco. Monday-Wednesday. 11.25 hrs. Fee: $270-300. Contact: American Society for Surgery of the Hand, 3025 S Parker Rd, Ste 65, Aurora, CO 80014.

January 19-23—**10th Annual Postgraduate Assembly in Surgery.** UCSD at US Grant Hotel, San Diego. Monday-Friday. 26.5 hrs. Fee: $275. Contact: UCSD.

January 22-24—**9th Annual Surgical Postgraduate Course.** UCD at Capitol Plaza Holiday Inn, Sacramento. Thursday-Saturday. 14 hrs. Contact: UCD.

January 25-31—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Sunday-Saturday. 62 hrs. Fee: $950. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

January 30-31—**Update on Uses of Lasers in Urology.** UCI at Long Beach. Friday-Saturday. Contact: UCI.

February 17-19—**Maxillofacial Trauma.** USC. Tuesday-Thursday. 16 hrs. Fee: $500. Contact: USC.

February 22-28—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Sunday-Saturday. 62 hrs. Fee: $950. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

March 5-8—**37th Annual Surgical Forum.** Society of Graduate Surgeons of Los Angeles County at Ambassador Hotel, Los Angeles. Thursday-Sunday. 25 hrs. Contact: Soc of Grad Surgeons, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

March 6-8—**Cruciate Ligament Surgery: Principles and Practice.** Scripps Clinic and Research Foundation at Marriott Hotel, La Jolla. Friday-Sunday. 23

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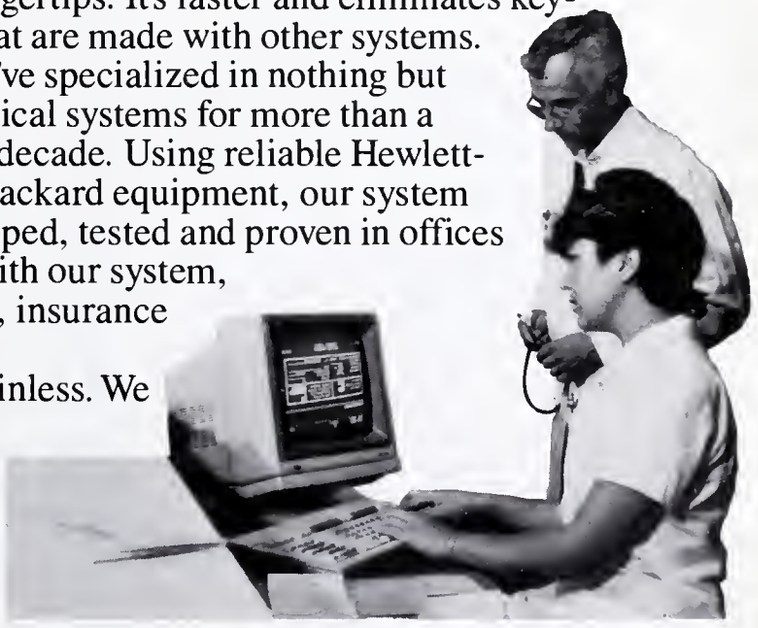

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Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

INTERPRETIVE MEDICAL MICROBIOLOGY—Edited by Harry P. Dalton, PhD, Professor, Department of Pathology and Microbiology, and Director, Clinical Microbiology Laboratories Medical College of Virginia, Virginia Commonwealth University, Richmond, and Harry C. Nottebart, Jr, JD, MD, Clinical Associate Professor, Department of Medicine, University of Virginia School of Medicine, Charlottesville, and Associate Clinical Professor, Department of Pathology, Medical College of Virginia, Virginia Commonwealth University, Richmond. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 1,040 pages, $115.

INVASIVE PROCEDURES IN CRITICAL CARE—Volume 7 in CLINICS IN CRITICAL CARE MEDICINE—Edited by Charles L. Sprung, MD, Associate Professor of Medicine, University of Miami School of Medicine, and Director, Section of Critical Care Medicine, Veterans Administration Medical Center, Miami, and Ake Grenvik, MD, Professor of Anesthesiology and Surgery, University of Pittsburgh School of Medicine, and Director, Critical Care Medicine, University Health Center Hospitals, Pittsburgh. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 282 pages, $39.

MANUAL AND ATLAS OF FINE NEEDLE ASPIRATION CYTOLOGY—Svante R. Orell, ML, FRCPA, FIAC, Associate Professor of Pathology and Direotor of Diagnostic Cytology, Flinders Medical Centre, Adelaide, South Australia; Gregory F. Sterrett, MBBS, FRCPA, MIAC, Pathologist, Hospital and University Pathology Services, The Queen Elizabeth II Medical Centre, Perth, Western Australia; Max N-I. Walters, MD, FRACP FRCPath, FRCPA, Professor of Pathology, University of Western Australia, and Director, Hospital and University Pathology Services, The Queen Elizabeth II Medical Centre, Perth, Western Australia, and Darrel Whitaker, PhD, CFIAC, FIMLS, AAIMLS, Cytologist, Hospital and University Pathology Services, The Queen Elizabeth II Medical Centre, Perth, Western Australia. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 232 pages, $139.

MANUAL OF ENDOCRINOLOGY AND METABOLISM—Norman Lavin, MD, Associate Clinical Professor of Pediatrics and Endocrinology, University of California, Los Angeles, School of Medicine, and Director of Perinatal and Pediatric Research, Endocrine Sciences Laboratory, Tarzana, California. Little, Brown and Company, 34 Beacon St, Boston, MA 02106, 1986. 719 pages, $19.50.

MEDICAL ASSESSMENT OF THE ELDERLY SURGICAL PATIENT—Gwyn Seymour, MB, ChB, BSci, MRCP(UK), Senior Lecturer in Geriatric Medicine, University of Wales College of Medicine. Aspen Systems Corporation, 1600 Research Blvd, Rockville, MD 20850, 1986. 315 pages, $37.50.

OB-GYN EMERGENCIES—THE FIRST 60 MINUTES—Edited by Roy G. Farrell, MD, Emergency Physician and Director, Walk-In Emergency Clinic, Group Health Medical Center, Seattle, and Assistant Clinical Professor of Medicine, University of California, Irvine. Aspen Publishers, Inc, 1600 Research Blvd, Rockville, MD 20850, 1986. 330 pages, $37.

ORTHOSTATIC HYPOTENSION—Irwin J. Schatz, MD, Professor and Chairman, Department of Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu. F. A. Davis Company, 1915 Arch Street, Philadelphia, PA 19103-1493, 1986. 126 pages, $30.

PATHOGENESIS OF SKIN DISEASE—Edited by Bruce H. Thiers, MD, Associate Professor of Dermatology, Medical University of South Carolina, and Chief, Dermatological Service, Veterans Administration Medical Center, Charleston, South Carolina, and Richard L. Dobson, MD, Professor and Chairman, Department of Dermatology, Medical University of South Carolina, Charleston, South Carolina. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 623 pages, $95.

PATHOPHYSIOLOGY OF ELECTROLYTE AND RENAL DISORDERS—Edited by H. David Humes, MD, Associate Chairman and Professor, Department of Internal Medicine, University of Michigan Medical School, and Chief, Medical Service, Veterans Administration Medical Center, Ann Arbor, Michigan. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 681 pages, $39 (paperback).

THE PERSISTING OSLER—Selected Transactions of the First Ten Years of the American Osler Society—Edited by Jeremiah A. Barondess, MD, Professer of Clinical Medicine, Cornell University Medical College, New York City; John P. McGovern, MD, McGovern Allergy Clinic, Texas Allergy Research Foundation, John P. McGovern Foundation, Houston, and Charles G. Roland, MD, Jason A. Hannah Professor of the History of Medicine, McMaster University Medical Center, Hamilton, Ontario. Aspen Systems Corporation, 1600 Research Blvd, Rockville, MD 20850, 1985. 318 pages, $45.

PHENYLPROPANOLAMINE—A CRITICAL ANALYSIS OF REPORTED ADVERSE REACTIONS AND OVERDOSAGE—John P. Morgan, MD, Professor and Director of Pharmacology, City University of New York Medical School. Jack K. Burgess, Inc, 2175 Lemoine Ave, Fort Lee, NJ 07024, 1986. 98 pages, $22.50.

PHYSICIAN-SPONSORED HMO DEVELOPMENT—Prepared by Erio R. Wagner and Valerie J. Hackenberg for the American Society of Internal Medicine. ASIM, 1101 Vermont Ave, NW, Suite 500, Washington, DC 20005, 1986. 63 pages, $10 (ASIM members), $15 (nonmembers).

PRACTICAL OBSTETRICAL ULTRASOUND—John W. Seeds, MD, Assistant Professor, and Robert C. Cefalo, MD, PhD, Professor, Department of Obstetrics and Gynecology, Division of Maternal and Fetal Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina. Aspen Publishers, Inc, 1600 Research Boulevard, Rockville, MD 20850, 1986. 185 pages, $33.50.

THE PROGRESSIVE NATURE OF RENAL DISEASE—Volume 14 in CONTEMPORARY ISSUES IN NEPHROLOGY—Edited by William E. Mitch, MD, Associate Professor of Medicine, Harvard Medical School, Brigham and Women's Hospital, and Barry M. Brenner, MD, Samuel A. Levine Professor of Medicine, Harvard Medical School, and Director, Renal Division and Laboratory of Kidney and Electrolyte Physiology, Brigham and Women's Hospital, Boston, and Jay H. Stein, MD, Professor and Chairman, Department of Medicine, and Director, Division of Renal Diseases, The University of Texas Health Science Center at San Antonio. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 283 pages, $55.

(Continued from Page 894)

hrs. Contact: Bonny A. Mower, Dept of Academic Affairs, Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

March 8-14—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Sunday-Saturday. 62 hrs. Fee: $950. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

March 18-20—**Preoperative Evaluation of the Surgical Patient.** UCSF at Holiday Inn Union Square, San Francisco. Wednesday-Friday. 16 hrs. Fee: $325. Contact: UCSF.

March 30-April 10—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Monday-Friday. 100 hrs. Fee: $1,750. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

April 11-18—**Surgery.** University of Washington at Royal Lahaina Hotel, Maui, Hawaii. One week. Contact: University of Washington School of Medicine, Div of CME, Sc-50, Seattle, WA 98195. (206) 543-1050.

April 30-May 2—**American Back Society Spring Symposium.** Anaheim Hilton Hotel. Thursday-Saturday. Contact: Aubrey A. Swartz, American Back Soc, 2647 E. 14th St, Ste 401, Oakland 94601. (415) 536-9929.

April 30-May 2—**Postgraduate Course in General Surgery.** UCSF at San Francisco. Thursday-Saturday. 15 hrs. Contact: UCSF.

May 11-15—**The San Francisco Orthopaedic Review Course.** UCSF at San Francisco. Monday-Friday. 40 hrs. Contact: UCSF.

May 13—**Otolaryngology: ENT Infections.** LLU at LLU. Wednesday. 4 hrs. Fee: $60. Contact: LLU.

OF INTEREST TO ALL PHYSICIANS

January 12-16—**Postgraduate Institute for Emergency and Primary Care Physicians.** UCSD at San Diego Hilton Hotel. Monday-Friday. 32 hrs. Fee: $325-400. Contact: UCSD.

January 16-17—**Cardiology for the Non-Cardiologist.** UCI at Long Beach. Friday-Saturday. 12.5 hrs. Contact: UCI.

January 16-18—**Gynecology Update for the Primary Care Physician.** UCSD at Vacation Village Resort, San Diego. Friday-Sunday. 15 hrs. Fee: $275. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 18-20—**Physical Examination of the Child Sexual Molest Victim: The State of the Art.** Children's Hospital, San Dicgo at Hanalei Hotel, San Diego. Sunday-Tuesday. 15.5 hrs. Fee: $200. Contact: Ann Albrecht, Children's Hospital, 8001 Frost St, San Diego 92123. (619) 576-1700.

January 18-23—**Nevada Academy of Family Physicians Winter Assembly: Living Healthier Longer.** Caesar's Tahoe Hotel and Casino, Nevada. Sunday-Friday. 34 hrs. Fee: $400. Contact: Dottie Batchelor, NAFP, PO Box 7471, Reno, NV 89510-7471. (702) 826-5100.

January 19-21—**Pediatrics for the Primary Care Physician.** UCSD at Vacation Village Resort, San Diego. Monday-Wednesday. 16 hrs. Fee: $275. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 20-24—**Intensive Course in Geriatric Medicine.** UCLA at Santa Monica. Tuesday-Saturday. 33 hrs. Contact: UCLA.

January 23-25—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** Continuing Medical Education Associates at San Diego. Friday-Sunday. 20 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

January 26-28—**Recent Advances in Geriatric Medicine: Nutrition and Drug Therapy.** UCSD at Holiday Inn Embarcadero, San Diego. Monday-Wednesday. 18 hrs. Fee: $395. Contact: UCSD.

January 28-30—**Neurology for Non-Neurologists.** UCSD at Holiday Inn Embarcadero, San Diego. Wednesday-Friday. 21 hrs. Fee: $375. Contact: UCSD.

January 30-February 1—**Primary Care Update—1987: A Practical Approach.** Scripps Clinic and Research Foundation at Vacation Village Resort, San Diego. Friday-Sunday. Fee: $200. Contact: Bonny Mower, Dept of Academic Affairs, PO Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

January 31-February 7—**Infectious Disease in General Medical and Pediatric Practice.** University of Colorado at Inter-Continental Hotel, Maui, Hawaii. One week. 24 hrs. Fee: $395. Contact: Univ of CO, Office of CME, 4200 E 9th Ave, Box C-295, Denver, CO 80262. (303) 394-5195.

February 2-7—**UCI Family Practice Refresher Course.** Newport Beach. Monday-Saturday. Contact: UCI.

February 2-7—**Sexual Science: Bridging the Discipline with the Master Clinicians.** UCLA at Mira-

mar-Sheraton Hotel, Santa Monica. Monday-Saturday. 12 hrs. Fee: $275. Contact: UCLA.

February 4-6—**4th Annual Practical Advances in Medicine.** Cypress Foundation at Carmel Mission Inn, Carmel. Wednesday-Friday. 16 hrs. Contact: Cypress Foundation, PO Box 80308, Salinas 93912. (408) 455-1833.

February 4-7—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Stanford Court Hotel, San Francisco. Wednesday-Saturday. 17 hrs. Contact: UCSF.

February 7-8—**2nd Triennial Diabetes Update.** Cypress Foundation at Hyatt Regency, Monterey. Saturday-Sunday. 10 hrs. Contact: Cypress Foundation, PO Box 80308, Salinas 93912. (408) 455-1833.

February 7-14—**Office Pediatrics for Primary Care Physicians.** University of Colorado at Kona Surf Hotel, Kona, Hawaii. One week. 20 hrs. Fee: $395. Contact: Univ of CO, Office of CME, 4200 E 9th Ave, Box C-295, Denver, CO 80262. (303) 394-5195.

February 8-11—**1987 Research Study Club Midwinter Conference.** Sheraton Grande Hotel, Los Angeles. Sunday-Wednesday. Fee: $235-275. Contact: Research Study Club, PO Box J, South Pasadena 91030.

February 9-14—**UCI Family Practice Refresher Course.** UCI at Newport Beach. Monday-Saturday. Contact: UCI.

February 13-15—**Office Gynecology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Islandia Hotel, San Diego. Friday-Sunday. 18 hrs. Fee: $275. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

February 21-28—**Radiology for Emergency and Primary Care Physicians.** Scripps Memorial Hospital, Encinitas at Royal Lahaina Resort, Maui, Hawaii. One week. 21 hrs. Fee: $375. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 23-27—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. Fee: $450. Contact: STAN.

March 4-6—**37th Annual Course for Physicians in Family Practice: Therapeutic Advances in Family Practice.** Mt Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Robin B. Jackson, Medical Staff and Education Office, Mt Zion Hospital, PO Box 7921, San Francisco 94120. (415) 885-7261.

March 6-12—**55th Annual Postgraduate Convention.** LLU Alumni Association at LLU. Friday-Thursday. 35 hrs. Contact: Carolyn Wieder, LLU, (714) 824-4633.

March 8—**Pharmacotherapeutic Interventions in the Treatment of Chemical Dependence—Drug Solutions for Drug Problems.** California Society for the Treatment of Alcoholism and Other Drug Dependencies at Anaheim. Sunday. Contact: Sandy Swift, Cal Soc for the Treatment of Alcoholism and Other Drug Dependencies, 3803 Broadway, #2, Oakland 94611. (415) 428-9091.

March 9-13—**Hawaii '87: Critical Issues in Primary Care.** Hawaii Medical Association at Waiohai Hotel, Poipu Beach. Monday-Friday. 20 hrs. Contact: Valerie Murray, Pacfic Institute of Continuing Medical Education, PO Box 1059, Koloa, Kauai, HI 96756. 1 (808) 742-7471.

March 13-15—**Office Emergencies in Primary Care.** Sharp Memorial Hospital at Hotel Del Coronado, Coronado. Friday-Sunday. 18 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

March 16-20—**Epidemics, Pandemics, and Mass Hysteria: From Antiquity to AIDS.** Kauai Foundation for Continuing Education at Poipu Beach, Kauai, Hawaii. Monday-Friday. 19 hrs. Contact: David J. Elpern, MD, Kauai Foundation for Continuing Education, PO Box 3650, Lihue, HI 96766. (808) 245-1507.

March 19-27—**Specialty Series in Primary Care: Cardiology, Infectious Diseases and Endocrinology.** UCSD at Palm Springs Spa Hotel. Thursday-Friday. Contact: UCSD.

March 26-28—**CPR Update/ACLS Recertification.** UCSF at Holiday Inn Union Square, San Francisco. Thursday-Saturday. Fee: $350. Contact: UCSF.

March 28—**Management of the Menopause: Osteoporosis and Estrogen Replacement Therapy.** Scripps Clinic and Research Foundation at La Jolla. Saturday. 7 hrs. Fee: $110. Contact: Bonny Mower, Dept of Academic Affairs, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

April 20-23—**Selected Topics in Dermatology and Pulmonary Intensive Care.** LLU at LLU. Monday-Thursday. 16 hrs. Fee: $400.

April 25-26—**Transurethral Ureteroscopy: A Seminar and Workshop.** UCSD at La Jolla Marriott Hotel, La Jolla. Saturday-Sunday. 13.5 hrs. Fee: $275-400. Contact: UCSD.

May 11-13—**Arthritis Update '87.** Sharp Memorial Hospital, San Diego and UCSD at Hyatt Islandia Hotel, San Diego. Monday-Wednesday. Contact: Mary Belich, Sharp Memorial Hospital, 7901 Frost St, San Diego 92123-2788. (619) 541-3400.

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December 27-January 3—**Advances in Internal Medicine.** Sun Valley. One week. Sponsor: University of Washington School of Medicine. Contact: U/W School of Medicine, Division of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 21-28—**Perinatal Medicine.** Sun Valley. One week. Sponsor: University of Washington School of Medicine. Contact: U/W School of Medicine, Division of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 27-March 1—**Personal Fitness for You and Your Patient: Speakers From the Cleveland Clinic.** Shore Lodge, McCall. Friday-Sunday. Sponsor: Ada County Medical Society. 11 hrs. Fee: $125. Contact: Judy Barningham, Ada County Medical Society, PO Box 2668, Boise 83701. (208) 336-2930.

March 14-21—**How to Make Fitness and Health Promotion Work in Your Practice.** Sun Valley. One week. 24 hrs. Sponsors: University of Arizona, Department of Family and Community Medicine, and Epic Medical Expeditions. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley 83353. (208) 788-4995.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

January 24-25—**Annual Family Practice Seminar.** Albuquerque. Saturday-Sunday. Marriott Hotel.

Presenting The Pacific Northwest's First Regional Seminar On Gerontological Nursing

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For the first time, more than 30 of the Pacific Northwest's leading specialists in the field of geriatric care join in a symposium aimed at making nurses and other health-care professionals more expert in caring for the elderly.

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Friday, January 30 and Saturday, January 31, 1987

Merritt Peralta Health Education Center
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CANCER UPDATE 1987 is a one and one-half day, no fee seminar sponsored by Peralta Hospital and the Medical Staff. Nine hours of formal Category I credit offered. Preregistration advised.

Call or write for registration information.

Education Department
Peralta Hospital
P.O. Box 23010
Oakland, CA 94623
(415) 451-4900. ext. 2327

Contact: New Mexico Chapter, American Academy of Family Physicians, PO Box 23070, Albuquerque 87192. (505) 298-5300.

February 5-7—**New Mexico-West Texas Urological Society—Annual Meeting.** Albuquerque. Thursday-Saturday. St Joseph Hospital. Contact: Edward L. Johnson, MD, 7000 Cutler NE, Albuquerque 87110. (505) 883-6230.

February 6-7—**Clinical Perspectives in Autoimmune Disease.** Albuquerque. Friday-Saturday. Sheraton Old Town. Contact: Arthritis Foundation, 7520 Montgomery NE, Ste E7, Albuquerque 87109. (505) 883-2964.

February 19-21—**Sports Medicine.** Tammaron. Thursday-Saturday. Contact: Lovelace Medical Foundation, Office of Medical Education, 2425 Ridgecrest Dr SE, Albuquerque 87108. (505) 262-7353.

February 20-22—**15th Annual Taos Lung Disease Symposium.** Taos. Friday-Sunday. Contact: NM Chapter, American Thoracic Society, 216 Truman NE, Albuquerque 87108. (505) 265-0732.

February 27-28—**Advances in Internal Medicine VII.** Albuquerque. Friday-Saturday. VAMC Conference Center. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

March 5-7—**20th Annual Ob/Gyn Postgraduate Seminar.** Albuquerque. Thursday-Saturday. Hilton. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

March 11-14—**New Mexico Metabolism Symposium.** Taos. Wednesday-Saturday. Quail Ridge Lodge. Contact: Lovelace Medical Foundation, Office of Medical Education, 2425 Ridgecrest Dr SE, Albuquerque 87108. (505) 262-7353.

March 14—**New Mexico Pediatric Society Wylder Lecture—Pediatric Neurology.** Albuquerque. Saturday. Contact: NM Pediatric Society, (505) 758-8651.

March 14—**Perfecting Your Cardiac Physical Diagnosis Techniques: Lessons From a Master—A Symposium by W. Proctor Harvey, MD.** Albuquerque. Saturday. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

March 19-20—**Cultural Issues in Family Therapy.** Albuquerque. Thursday-Friday. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

April 9-11—**9th Annual Pediatric Cardiopulmonary Update.** Albuquerque. Thursday-Saturday. AMFAC Hotel. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

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(Continued from Page 900)

April 24-25—**Practical Orthopaedics in the Primary Care Setting.** Albuquerque. Friday-Saturday. Veterans Administration Medical Center. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

May 6-8—**New Mexico Medical Society—Annual Meeting.** Albuquerque. Wednesday-Friday. Clarion Four Seasons. Contact: NMMS, 303 San Mateo NE, #204, Albuquerque 87108. (505) 266-7868.

May 15-16—**Biological and Ethical Dimensions of Human Transplantation.** Albuquerque. Friday-Saturday. Contact: Office of Medical Education, Presbyterian Hospital, PO Box 26666, Albuquerque 87125. (505) 841-1225.

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave, Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 W Harvard Ave, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 W Harvard Ave, Roseburg 97470. (503) 673-6641.

Emanuel Hospital, 2801 N Gantenbein St, Portland 97227:

Every Friday, 12:15 p.m. to 1:00 p.m. **Medical Grand Rounds.** Contact: Philippa McClure, Emanuel Hospital, 2801 N Gantenbein St, Portland 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Ave, Portland 97210:

Every Tuesday, 12:00 noon to 1:00 p.m. **Medicine Grand Rounds.** Neurological Sciences Buildings, First Floor Auditorium. Contact: Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Ave, Portland 97201. (503) 229-7454.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder St, Eugene 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene 97440.

Salem Hospital, 665 Winter St SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St SE, Salem 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St SE, Salem 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St Vincent Hospital & Medical Center, 9205 SW Barnes Rd, Portland 97225. (503) 297-4411, Ext 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept of Psychiatry, Oregon Health Sciences University, Portland 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept of Medicine, Oregon Health Sciences University, Portland 97201. (503) 225-8607.

(Continued on Page 910)

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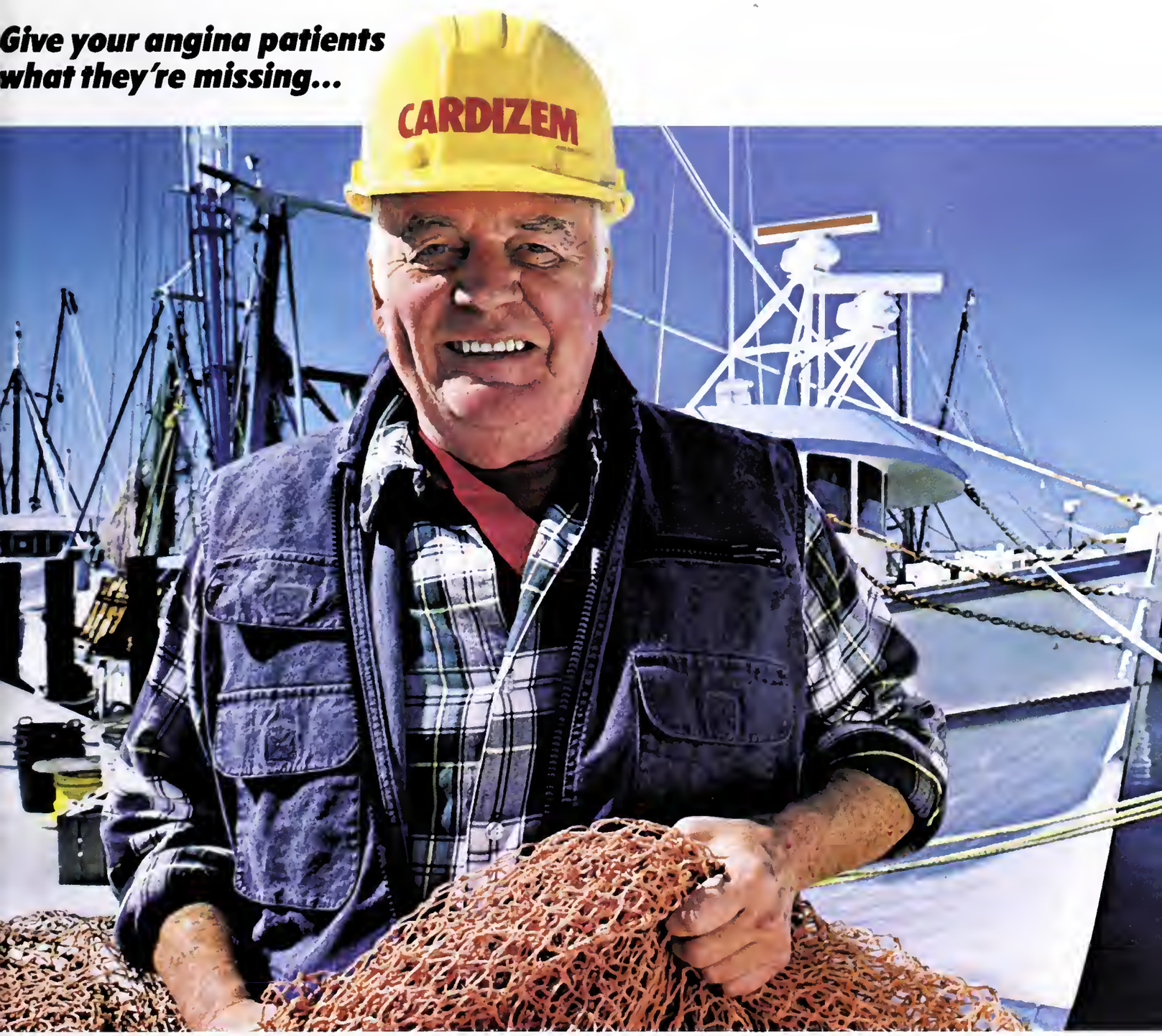

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- ***A safe choice for angina patients with coexisting hypertension, asthma, COPD, or PVD[4,5]***

***See Warnings and Precautions.**

Please see brief summary of prescribing information on the next page.

CARDIZEM® FEW SIDE EFFECTS IN ANTIANGINAL THERAPY

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Brief Summary
Professional Use Information

CARDIZEM®
(diltiazem HCl) 30 mg and 60 mg Tablets

CONTRAINDICATIONS
CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. ***Cardiac Conduction.*** *CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.*
2. ***Congestive Heart Failure.*** *Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt).*
   Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. ***Hypotension.*** *Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.*
4. ***Acute Hepatic Injury.*** *In rare instances, significant elevations in enzymes such as alkaline phosphatase, CPK, LDH, SGOT, SGPT, and other symptoms consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)*

PRECAUTIONS
General. *CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes, however, these changes were reversible with continued dosing.*

Drug Interaction. *Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)*

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. *A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.*

Pregnancy. *Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration at doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.*

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. *Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.*

Pediatric Use. *Safety and effectiveness in children have not been established.*

ADVERSE REACTIONS
Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	*Angina, arrhythmia, AV block (first degree), AV block (second or third degree — see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.*
Nervous System:	*Amnesia, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.*
Gastrointestinal:	*Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.*
Dermatologic:	*Petechiae, pruritus, photosensitivity, urticaria.*
Other:	*Amblyopia, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.*

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

Issued 7/86

See complete Professional Use Information before prescribing.

References: ***1.*** *Pepine CJ, Feldman RL, Hill JA, et al: Clinical outcome after treatment of rest angina with calcium blockers. Comparative experience during the initial year of therapy with diltiazem, nifedipine, and verapamil. Am Heart J 1983, 106(6):1341-1347.* ***2.*** *Shapiro W: Calcium channel blockers: Actions on the heart and uses in ischemic heart disease. Consultant 1984;24(Dec):150-159.* ***3.*** *Johnston DL, Lesaway R, Humen DP, et al: Clinical and hemodynamic evaluation of propranolol in combination with verapamil, nifedipine and diltiazem in exertional angina pectoris: A placebo-controlled, double-blind, randomized, crossover study. Am J Cardiol 1985;55:680-687.* ***4.*** *Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39.* ***5.*** *Schroeder JS: Calcium and beta blockers in ischemic heart disease. When to use which. Mod Med 1982;50(Sept):94-116.*

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KANSAS CITY, MO 64137

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CONFIRMED

CONFIRMED BY CLINICAL EVIDENCE

ZANTAC® 150 h.s.

ranitidine HCl/Glaxo 150 mg tablets

EFFECTIVE MAINTENANCE THERAPY

for healed duodenal ulcer patients

CONFIRMED

In two randomized, double-blind, and well-controlled clinical trials, ZANTAC 150 mg h.s. significantly superior to cimetidine 400 mg h.s. for maintenance therapy in healed duodenal ulcers.

Percent of patients with observed duodenal ulcer recurrence

		0-4 months	0-8 months	0-12 months	No. patients
USA[1]	ranitidine 150 mg h.s.	9%	14%*	16%†	60
	cimetidine 400 mg h.s.	23%	34%	43%	66
UK, Ireland, Australia[2]	ranitidine 150 mg h.s.	8%‡	14%‡	23%‡	243
	cimetidine 400 mg h.s.	21%	34%	37%	241

*p=0.02
†p=0.01
‡p≤0.004
%=life-table estimates
All patients were permitted prn antacids for relief of pain.

These two trials used the currently recommended dosing regimen of cimetidine (400 mg h.s.) and ranitidine (150 mg h.s.). A comparison of other dosing regimens has not been studied.

The studied dosing regimens are not equivalent with respect to the degree and duration of acid suppression or suppression of nocturnal acid.

The superiority of ranitidine over cimetidine in these trials indicates that the dosing regimen currently recommended for cimetidine is less likely to be as successful in maintenance therapy.

Convenient once-a-night dose with a

low incidence of side effects[3]

Headache, sometimes severe, seems to be related to ranitidine administration. Other side effects have been reported; for a complete listing, see the **ADVERSE REACTIONS** section in the Brief Summary.

No significant interference with the hepatic cytochrome

P-450 enzyme system at recommended doses

ZANTAC 150 mg has no significant drug interactions with theophylline, phenytoin, or warfarin. The bioavailability of certain medications whose absorption is dependent on a low gastric pH may be altered when ZANTAC or other medications that decrease gastric acidity are administered.

Zantac® 150

ranitidine HCl/Glaxo 150 mg tablets

One tablet at bedtime
for maintenance

See next page for references and
Brief Summary of Product Information.

Glaxo / ROCHE®

CONFIRMED

Zantac® 150

ranitidine HCl/Glaxo 150 mg tablets

One tablet at bedtime for maintenance therapy in healed duodenal ulcer patients

References:

1 Silvis SE, Griffin J, Hardin R, et al: Final report on the United States multicenter trial comparing ranitidine to cimetidine as maintenance therapy following healing of duodenal ulcer. *J Clin Gastroenterol* 1985;7(6):482-487

2 Gough KR, Korman MG, Bardhan KD, et al: Ranitidine and cimetidine in prevention of duodenal ulcer relapse: A double-blind, randomised, multicentre, comparative trial. *Lancet* 1984;ii:659-662.

3 Data available on request, Glaxo Inc.

ZANTAC® 150 Tablets
(ranitidine hydrochloride)
ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY OF PRODUCT INFORMATION

See complete product information before prescribing. The following is a brief summary

INDICATIONS AND USAGE: ZANTAC® is indicated in:

1. Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer, active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy. 2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function. Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: *Teratogenic Effects: Pregnancy Category B:* Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established

Use in Elderly Patients. Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with oral ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Rare reports of reversible leukopenia, granulocytopenia, thrombocytopenia, and pancytopenia.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumental: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison Syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day

See full prescribing information for dosage adjustment for patients with impaired renal function.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

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June 1986

Glaxo

Glaxo Inc.
Research Triangle Park, NC 27709

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(Continued from Page 902)

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland 97201. (503) 225-7590.

FAMILY PRACTICE

February 9-13—**18th Annual Family Practice Review.** Portland. Monday-Friday. Marriott Hotel. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

January 23—**Infectious Disease Symposium.** Portland. Friday. OHSU Campus. Contact: OHSU-CME.

February 26-March 1—**Update in Rheumatology.** Bend. Thursday-Sunday. Inn of the Seventh Mountain. Contact: OHSU-CME.

March 2-6—**MKSAP VII Review Course.** Portland. Monday-Friday. Red Lion/Lloyd Center. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

January 5-14—**Hip and Knee Bioskills Workshop** (Sponsor: UUMC). 10 days. Snowbird Resort. 15 hrs. Contact: Aaron Hoffman, MD, (801) 581-8664.

January 20-22—**Pulmonary Function Testing** (Sponsor: UUMC). Tuesday-Thursday. RMCOEH, University of Utah. 18 hrs. Contact: Connie Crandall, (801) 581-8719.

February 1-6—**Diagnostic Imaging/Interventional Radiology** (Sponsor: UUMC). Sunday-Friday. Snowbird Resort. 20 hrs. Contact: Judy Gallegos, (801) 581-8188.

February 9—**Stress, Emotion and Heart Disease** (Sponsor: UUMC). Monday. Westin Hotel Utah, Salt Lake City. 6 hrs. Contact: Hilmon Castle, MD, (801) 581-8664.

February 10-13—**Family Practice Refresher Course** (Sponsor: UUMC). Tuesday-Friday. Westin Hotel Utah, Salt Lake City. 28 hrs. Contact: Denise Denton, (801) 581-5224.

February 11-14—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wednesday-Saturday. Salt Lake City. 17 hrs. Contact: (801) 521-1221.

February 12-14—**Rigid Fixation Techniques/Craniomaxillofacial Surgery** (Sponsor: UUMC). Thursday-Saturday. Snowbird Resort. 20 hrs. Contact: Louis Morales, MD, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143, (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

February 14-21—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). One week. Park City Resort. 25 hrs. Contact: John Matsen, MD, (801) 581-7480.

February 19-21—**Mid-Winter Trauma Seminar for Military and Civilians** (Sponsor: UUMC). Thursday-Saturday. Westin Hotel Utah, Salt Lake City. 15 hrs. Contact: Clayton Petty, MD, (801) 581-6393.

February 20-24—**Postgraduate Course in Anesthesiology** (Sponsor: UUMC). Friday-Tuesday. Salt Lake City. 16 hrs. Contact: Theodore Stanley, MD, (801) 581-6393.

February 21-25—**Annual Ob-Gyn Update** (Sponsor: UUMC). Saturday-Wednesday. Park City. 15 hrs. Contact: James Scott, MD, (801) 581-5501.

February 22-27—**Park City Dermatology Seminar** (Sponsor: UUMC). Sunday-Friday. Park City. 18 hrs. Contact: Gerald Kruegar, MD, (801) 581-7837.

February 23-27—**Surgical Pathology Workshops** (Sponsor: UUMC). Monday-Friday. The Yarrow, Park City. 20 hrs. Contact: Tom Colby, MD, (801) 581-7480.

February 25-28—**Gynecologic Oncology** (Sponsor: UUMC). Wednesday-Saturday. Park City. 15 hrs. Contact: James Scott, MD, (801) 581-5501.

February 26-28—**Arthroscopic Surgery** (Sponsor: UUMC). Thursday-Saturday. Westin Hotel Utah, Salt Lake City. 21 hrs. Contact: Robert Metcalf, MD, (801) 581-7601.

March 2-6—**Advances in Internal Medicine.** (Sponsor: UUMC). Monday-Friday. Snowbird Resort. 25 hrs. Contact: Malcolm Berenson, MD, (801) 581-7801.

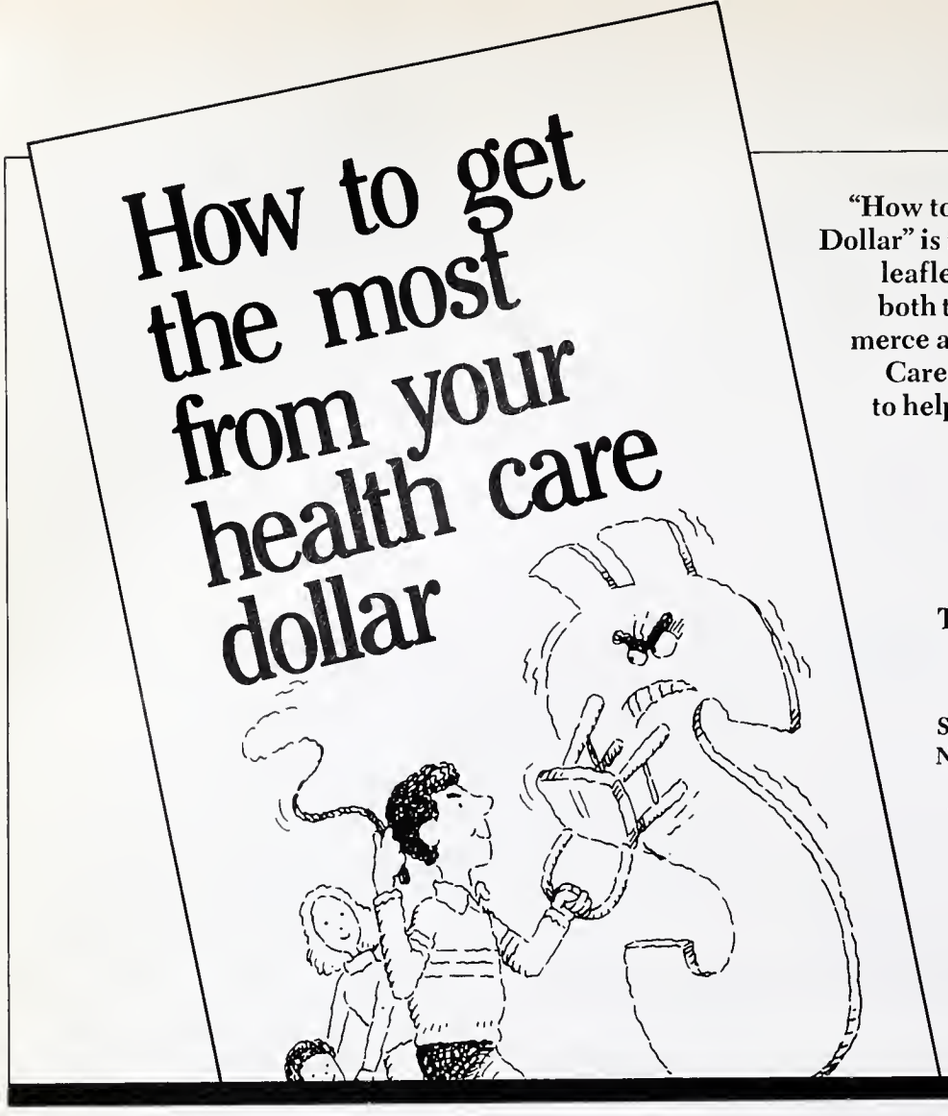
March 8-13—**Diagnostic Imaging and Interventional Radiology** (Sponsor: UUMC). Sunday-Friday. Snowbird Resort. 20 hrs. Contact: Judy Gallegos, (801) 581-8188.

March 9-13—**Medical and Surgical Advances in GI** (Sponsor: UUMC). Monday-Friday. Snowbird Resort. 25 hrs. Contact: Malcolm Berenson, MD, (801) 581-3581.

March 9-14—**Advanced Rheumatology 1987** (Sponsor: UUMC). Monday-Saturday. Snowbird Resort. 20 hrs. Contact: John Ward, MD, (801) 581-8664.

March 11-13—**9th Annual Common Problems in Pediatrics** (Sponsor: UUMC). Wednesday-Friday. Salt Lake Hilton. 14 hrs. Contact: Katharine Blosch, (801) 466-3500.

March 16-20—**Nutrition in Contemporary Medicine** (Sponsor: UUMC). Monday-Friday. Park City. 30 hrs. Contact: Malcolm Berenson, MD, (801) 581-3581.



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CONTINUING MEDICAL EDUCATION

March 26-28—**Neurology for the Practitioner** (Sponsor: UUMC). Thursday-Saturday. Salt Lake City. 15 hrs. Contact: Richard Baringer, MD, (801) 581-8664.

April 6-8—**Genetic Testing and New Biomedical Technologies in the Prevention of Occupational and Environmental Disease** (Sponsor: UUMC). Monday-Wednesday. Park City. 18 hrs. Contact: Connie Crandall, (801) 581-8719.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

January 14—**Occupational Medicine.** Seattle. Wednesday. Contact: Northwest Hospital, Education & Training Dept, 1550 N 115th St, Seattle 98133. (206) 364-0500, ext 1621.

January 15-16—**Agricultural Health and Safety.** Seattle. Thursday-Friday. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

January 21—**Ectopic Gestations and Implementation Failures.** Seattle. Wednesday. U/W Health Sciences. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 623-4801.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

(Continued on Page 915)

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MD NEEDS—SOUTHERN CALIFORNIA ONLY—FPs, GP, IM, OB/GYN, OR and other subspecialties needed for private groups and associations. Baker, Ellerd and Associates, Inc., 16200 Ventura Blvd., Ste. 426, Encino, CA 91436; call (818) 995-4311.

INTERNAL MEDICINE—Multispecialty group needs additional Internists. A growing group in a dynamic Southwest community; excellent practice; benefits; and investment opportunities. Send CV to: D. R. Molesworth, Administrator, The Tucson Clinic, P.C., PO Box 26926, Tucson, AZ 85726.

OTOLARYNGOLOGIST. Position available with 35-member multispecialty group; BC/BE; immediate opening; full range of benefits plus immediate shareholder status; excellent opportunity; central coast of California. Respond with CV to: Colin J. Wells, MD, San Luis Medical Clinic, Ltd., 1235 Osos St., San Luis Obispo, CA 93401-3619. No phone calls please.

CALIFORNIA. BC/BE Pediatrician and Internist to join young group at the edge of the Sierras. Send CV to Number 149, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

BUSY FEMALE GYN looking for quality associate. Excellent opportunity in suburban Los Angeles for BC/BE OB/GYN. Full- or part-time. Gynecology only, but great potential for full Obstetrics practice if desired. Position available immediately. Must be sensitive, well-trained, personable, and hard-working man or woman. Please reply to Number 152, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PHYSICIANS WANTED

INTERNIST BC/BE—Opening for General Internist in a 32-physician, multispecialty group located in the Pacific Northwest. Guaranteed salary and immediate full participation in incentive program, plus outstanding benefit package. Please submit your CV to the Search Committee, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

PEDIATRICIAN: The San Luis Medical Clinic, Ltd. a 35-member multispecialty group practicing on the California central coast has an immediate need for a general Pediatrician. Full range of benefits and all practice costs paid. Send CV to: Colin J. Wells, MD, San Luis Medical Clinic Ltd., 1235 Osos St., San Luis Obispo, CA 93401-3619. No telephone calls please.

FAMILY PRACTICE. Position available with 35-member multispecialty group; BC/BE; immediate opening; full range of benefits plus immediate shareholder status; excellent opportunity; central coast of California. Respond with CV to: Colin J. Wells, MD, San Luis Medical Clinic, Ltd., 1235 Osos St., San Luis Obispo, CA 93401-3619. No phone calls please.

NEW MEXICO—Primary Care Physician for 600-bed psychiatric/geriatric hospital in Las Vegas, New Mexico. Competitive salaries and generous benefits including on-call compensation. Superb climate and nearby recreational facilities. Contact: Medical Director, Las Vegas Medical Center, PO Box 1388, Las Vegas, NM 87701-1388 or call (505) 425-6711, ext. 5402.

OB/GYN position available with 35-member multispecialty group; BC/BE; immediate opening; full range of benefits plus immediate shareholder status; excellent opportunity; central coast of California. Respond with CV to: Colin J. Wells, MD, San Luis Medical Clinic, Ltd., 1235 Osos St., San Luis Obispo, CA 93401-3619. No phone calls please.

FAMILY PRACTICE opportunities available in New Mexico communities. Financial assistance available; excellent weather in the Sunbelt. For further information, please submit CV to: Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or, call 1 (800) 545-4030, Ext. 8300.

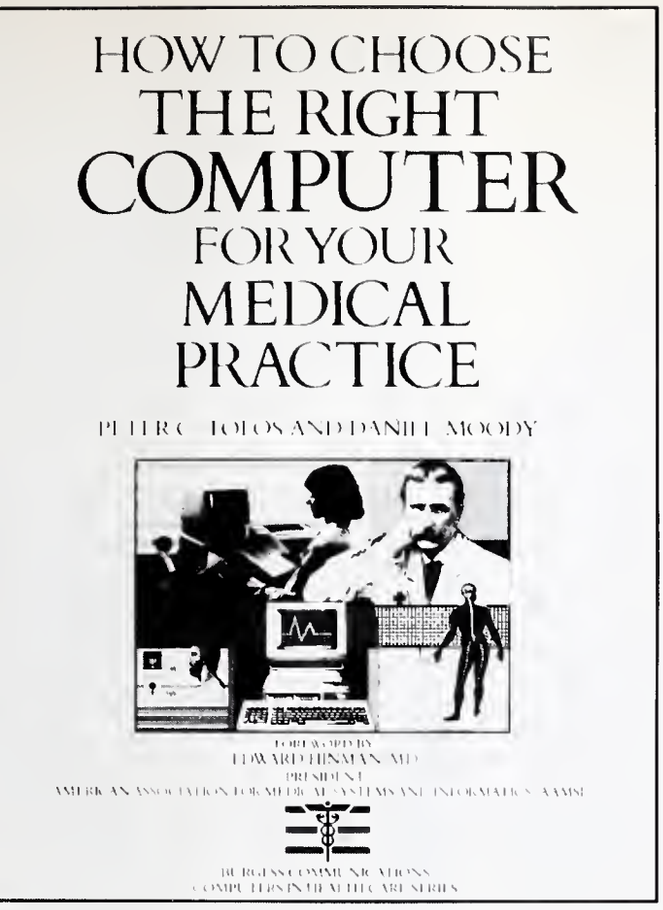
ASSISTANT PROFESSOR

The Department of Medicine (Gastroenterology), University of California, San Francisco, seeks an outstanding academician at the Assistant Professor (in Residence) level to join the Liver Center Laboratory at San Francisco General Hospital. The Laboratory is oriented to basic approaches to understanding liver disease, with emphasis on liver cell biology and molecular mechanisms of hepatic inflammation and fibrosis.

Applicants should have a strong research commitment and evidence of productivity in the general areas described above and specifically in the area of extracellular matrix metabolism.

Applicants should be accomplished clinicians, Board eligible or certified in internal medicine and gastroenterology, with demonstrated excellence in patient-care and teaching. The position will entail a time commitment of 70% to 80% to laboratory research and 20% to 30% to teaching at San Francisco General Hospital. Send curriculum vitae, a summary of current research, a concise outline of future research and three letters of reference by February 1, 1987 to D. Montgomery Bissell, MD, Search Committee Chair, Rice Liver Center, Building 40, Rm. 4102, San Francisco General Hospital, 1001 Potrero Ave., San Francisco, CA 94110. UCSF is an Equal Opportunity/Affirmative Action Employer. Women and minorities are encouraged to apply.

(Continued on Page 916)



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CONTINUING MEDICAL EDUCATION

(Continued from Page 912)

January 23—**Topics in Pulmonary Medicine: Interstitial Lung Disease.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

January 30—**Alternative Delivery and Financing Systems: Your Options and How to Evaluate Them.** Seattle. Friday. Contact: AMA, Dept of Practice Management, 535 N Dearborn St, Chicago, IL 60610. (312) 645-4958.

January 31—**Management of Psychotic Patient in the Office Setting.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

February 4-6—**Spirometry Training for Worker Screening.** Seattle. Wednesday-Friday. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

February 5-6—**Aging and the Elderly.** Seattle. Thursday-Friday. Contact: U/W.

February 6-7—**Modern Concepts in Allergy.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 11—**Vocational Rehabilitation.** Bellevue. Wednesday. Contact: U/W.

February 11—**Lifestyles.** Seattle. Wednesday. Contact: Northwest Hospital, Education & Training Dept, 1550 N 115th St, Seattle 98133. (206) 364-0500, ext 1621.

February 11-13—**Vocational Rehabilitation Conference.** Seattle. Wednesday-Friday. Contact: U/W.

February 19-20—**Sexual Assault: Advances in Medical-Legal Issues.** Seattle. Thursday-Friday. Contact: Sexual Assault Center, Harborview Medical Center, 325 Ninth Ave, Seattle 98104. (206) 223-3047.

February 20-21—**Office Gynecology for the Primary Care Physician.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 26-27—**Health and Safety of Firefighters.** Seattle. Thursday-Friday. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

March 13—**Recent Developments in Occupational Medicine.** Seattle. Friday. NW Center for Occupational Health and Safety. Contact: U/W Dept of

(Continued on Page 919)

(Continued from Page 914)

PHYSICIANS WANTED

CHIEF OF INTERNAL MEDICINE (Physician III)—$6,151-$6,504/monthly. Applications are being accepted for the Chief of Internal Medicine with the County Hospital. Natividad Medical Center is a 204-bed teaching hospital affiliated with the University of California, San Francisco for a family practice residency program. Excellence in teaching and administrative experience required along with Board certification. For applications and further information, submit CV to Ray K. Bolinger, Hospital Administrator, Natividad Medical Center, PO Box 8-1611, Salinas, CA 93912-1611; or phone (408) 757-0585. FFD until sufficient applications are received.

NORTHERN CALIFORNIA, EMERGENCY MEDICINE. Full-time positions available in the Emergency Room at The University of California Davis Medical Center. The University serves a large region of Northern California and is a major trauma center. Emergency physicians teach and supervise medical students and housestaff in addition to treating patients, primarily. Opportunities exist for involvement in other School of Medicine teaching activities. Applicants should send curriculum vitae to Robert W. Derlet, MD, University of California Davis Medical Center, 2315 Stockton Blvd., Department of Emergency Medicine, Trailer 1219, Sacramento, CA 95817.

TALENTED INTERNIST full-time in private practice with four other Internists covering rural ER/Acute medicine. Involves four two night shifts per month. Scheduling flexible. Sense of humor preferred. 60K. C. Rath, MD, 199 E. Webster St., Colusa, CA 95932; (916) 458-7739.

FAMILY PRACTICE PHYSICIAN/MEDICAL DIRECTOR. (Scenic Northwest) Two positions available: Family Practice Physician and Physician/Medical Director. Must be Family Practice physician BC/BE. System of four primary care community clinics. Full-scope family practice, hospital and SIF privileges. New facilities, excellent salary and fringes. Send résumé to: Community Health Care Delivery Systems FC-3312, 3629 South D St., Tacoma, WA 98408. EOE.

FAMILY PHYSICIAN, BC or BE, residency-trained, to join two very busy young FP's in Phoenix, Arizona, July 1987. No OB. Excellent income. Great city. 310 days of sunshine. Contact G. A. Rada, MD, 12251 N. 32nd St., Ste. 4, Phoenix, AZ 85032; (602) 992-1900.

HAWAII. ER PHYSICIAN NEEDED. Full-time, permanent, career position on Kauai. Part of 36-physician multispecialty group. Salary $50-$70K, plus vacation, CME, and complete benefit package. 1,000 visits/month. Full stockholder in 1-2 years. Six ER physicians share shifts evenly. Surfing, diving, fishing, hunting, rodeo, sailing, windsurfing, dirt-biking and polo. Tail covered 100% at end of 5 years. This is a peach, don't hesitate. (Board eligible strongly preferred.) Please submit CV to: James Scamahorn, MD, Kauai Medical Group, 3420-B Kuhio Highway, Lihue, HI 96766. Phone: (808) 245-1012.

SAN FRANCISCO, EMERGENCY MEDICINE. Part-time and full-time positions available in busy emergency department (32,000 patient visits/year) in full service hospital with excellent in-house specialty back-up. Prefer ABEM or ABIM certified/eligible, experienced Emergency Physician. Competitive salary, excellent benefits. Call or write Pat Salber, MD, Kaiser Permanente Medical Group, 2200 O'Farrell St., San Francisco, CA 94115; (415) 929-4020.

CALIFORNIA: Openings for emergency department Medical Directors and full-time staff physicians are immediately available at two client hospitals in California. Guaranteed rate of compensation, occurrence malpractice insurance coverage, flexible scheduling, CME allowance, plus more. For additional details contact Bill Salmo, Spectrum Emergency Care, 6275 Lehman Dr., Ste. C202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

PHYSICIANS WANTED

Listen to
Opportunity Knocking

38-Bed Hospital With
62-Bed Long-term Care Facility
Patient-to-Doctor Ratio = 3,750 to 1
(Highest Ratio in Oklahoma)
Opening for
Family Practitioner, General Surgeon
Rural Community, Excellent Schools
5 Hours From Ski Slopes

Contact: L. V. Melton, Administrator
Beaver County Memorial Hospital
Box 640
Beaver, Oklahoma 73932
(405) 625-4551

ACADEMIC EMERGENCY MEDICINE—The University of California, Davis, School of Medicine is recruiting for a full-time faculty position at the Assistant or Associate Professor level to serve in the Division of Emergency Medicine and Clinical Toxicology. The UCD Emergency Department provides comprehensive emergency care and is a major trauma center. Candidates must be Board certified in Emergency Medicine or Internal Medicine with experience in emergency medicine, and be eligible for licensure in California. The candidate must have prior academic and clinical experience in emergency medicine. Experience in clinical toxicology is highly desirable. A letter outlining research, teaching background and interests, experience, a curriculum vitae and the names of five references must be received by February 28, 1987. Reply to: Robert W. Derlet, MD, Chair of Emergency Medicine Search Committee, Department of Internal Medicine, University of California Davis Medical Center, 2315 Stockton Blvd., Sacramento, CA 95817. The University of California is an Affirmative Action/Equal Opportunity Employer.

URGENT CARE CENTER. Arizona, Phoenix and Tucson areas. Opportunity for physician with Family Practice or IM background in hospital-affiliated urgent care centers. Please send CV to: Executive Director—Urgent Care, Mercy Services Corporation-Phoenix, 350 W. Thomas Rd., Phoenix, AZ 85013.

VASCULAR GENERAL SURGEON—To associate with senior Surgeon. Well established referral practice. Salary plus percentage. Central California. Send curriculum vitae to Number 165, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

OB/GYN—Excellent private practice opportunity with income guarantee in the resort community of Ruidoso, New Mexico. Please submit CV to: Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or, call 1 (800) 545-4030, Ext. 8300.

NONINVASIVE CARDIOLOGIST—BC/BE to join busy invasive cardiologist. Early partnership. Expertise required in all noninvasive activities including: nuclear cardiology, 2D-Doppler and echo. Also, Swan-Ganz and pacemaker insertion. In Santa Clara Valley, California. Please send curriculum vitae to Number 163, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

MEDICAL ONCOLOGY FELLOWSHIP—CALIFORNIA. Starting in July, 1988, 2 or 3 year training programs at City of Hope Medical Center in Duarte, California are available. Candidates must be board eligible in internal medicine and eligible for California licensure; individuals with a strong interest in an expanding research program in cancer pharmacology are encouraged to apply. Inquiries should be sent to: Dr Lucille A. Leong, Dept. of Medical Oncology, 1500 E. Duarte Rd., Duarte, CA 91010, or telephone Dr Leong at (818) 359-8111.

PHYSICIANS WANTED

FAMILY PRACTICE. Steinbeck Country, BC/BE FP to join dynamic group; includes hospital care, OB, shared call. Spanish helpful. Many visiting consultants, good guarantee with chance for early partnership. Many fringes. One hr. to Monterey, three hrs. to S.F. Call or write: Helen Poole, 210 Canal St., King City, CA 93930; (408) 385-5471.

WORK PART TIME: Position available for Internist or GP/FP with Internal Medicine experience in Primary Care Practice, northern California Sierra foothills community of 25,000. Share rotating practice with two other MDs; you work one week in three. Outpatient and inpatient responsibiliies (no OB, no ICU) in modern, fully equipped 100 bed hospital. Minimum salary of $1,800/week (with incentives, actual will be around $2,200/week). Insurance, housing, and meals provided N/C. Send CV to: David Lomba, 133 'B' Ascot Ct., Moraga, CA 94556.

STAFF PSYCHIATRISTS. Fresno County is accepting applications for two physicians to fill contract positions in Mental Health Services. Work as a psychiatric consultant on a treatment team with other professionals in a variety of outpatient and inpatient settings. California license and completion of approved psychiatric residency required. Contract salary range $62,000 to $68,000, plus extra pay for inpatient assignment, weeknight or weekend coverage (on rotation with 10 or more psychiatrists). Benefits include: 5 weeks unscheduled time (vacation, sick leave, CME) and 10 paid holidays. Send résumé and copy of California license to Robert A. Kinsey, MD, Medical Director, Fresno County Department of Health, PO Box 11867, Fresno, CA 93775; (209) 453-4024.

INTERNAL MEDICINE—BE/BC. Suburban opportunity to join established practice adjacent to new 123 bed hospital in community of 100,000. Excellent referral patterns with emphasis on critical care medicine and gastroenterology. Send CV to: 11522 Sunview CR., Spokane, WA 99206.

BEAUTIFUL MOUNTAIN SETTING—BC/BE General Internist needed in rapidly expanding, thriving internal medicine practice in northwest Montana. Wide range of clinical opportunities offered with virtually unlimited recreational opportunities including skiing, hiking, fishing in immediate wilderness surroundings. Send CV to Dr Robert Patton, 418 Maine Ave., Libby, MT 59923; (406) 293-7758.

SAN FRANCISCO/MARIN COUNTY: Large multispecialty group needs ENT, Orthopedist, Ophthalmologist. Guarantee plus incentive plus benefits. Contact: Western Physicians Registry, Carol Sweig, Director, (415) 826-7676, 1315 Evans Ave., San Francisco, CA 94124.

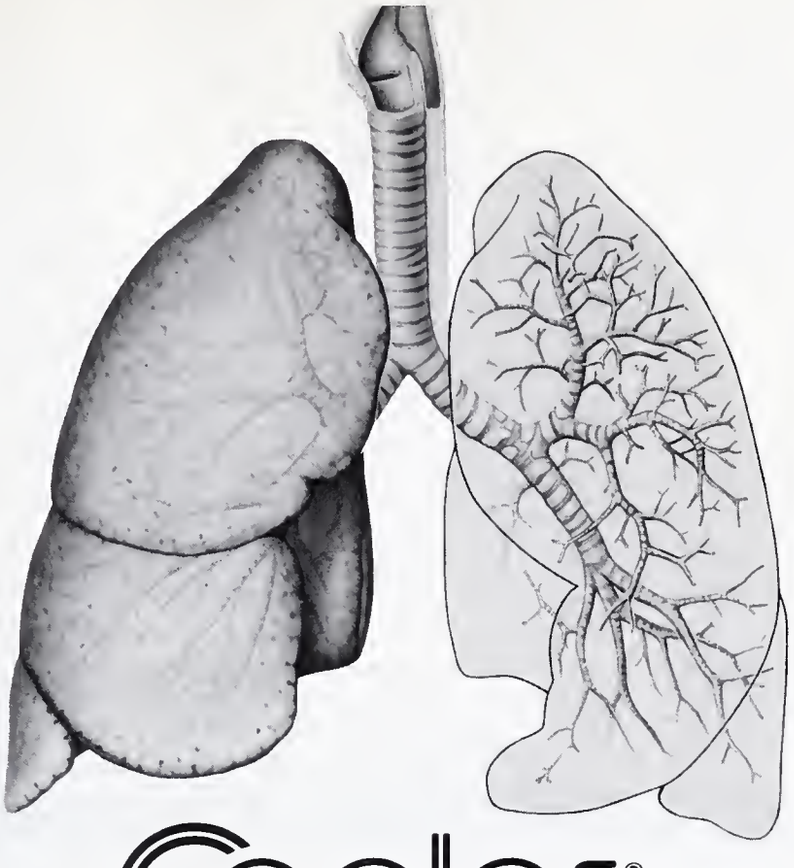
ORTHOPEDIC SURGEON to join established, growing multispecialty group in Marin County. Board certified/eligible required. This group of 58+ physicians provides care to both fee-for-service and prepaid patients. Excellent practice opportunity and superb living conditions. Guaranteed starting salary with ownership potential. Send CV to: Ross Valley Medical Clinic, Inc., 1350 S. Eliseo Dr., Greenbrae, CA 94904, Attn: Personnel.

ENT SPECIALIST to join established, growing multispecialty group in Marin County. Board certified/eligible required. This group of 58+ physicians provides care to both fee-for-service and prepaid patients. Excellent practice opportunity and superb living conditions. Guaranteed starting salary with ownership potential. Send CV to: Ross Valley Medical Clinic, Inc., 1350 S. Eliseo Dr., Greenbrae, CA 94904, Attn: Personnel.

RHEUMATOLOGIST. 48 physician multispecialty medical group seeks full-time BE/C Rheumatologist. Attractive compensation and benefits. Starting date negotiable. Send CV to Don Robertson, Administrator, The Moore-White Medical Group, 266 S. Harvard Blvd., Los Angeles, CA 90004.

(Continued on Page 918)

Consider the causative organisms...



Ceclor®
cefaclor

250-mg Pulvules® t.i.d. offers effectiveness against the major causes of bacterial bronchitis

Haemophilus influenzae, H influenzae, Streptococcus pneumoniae, Streptococcus pyogenes
(ampicillin-susceptible) (ampicillin-resistant)

Note: Ceclor® is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

Ceclor® (celaclor)

Summary. Consult the package literature for prescribing information.

Indications: Lower respiratory infections, including pneumonia, caused by susceptible strains of *Streptococcus pneumoniae, Haemophilus influenzae,* and *S. pyogenes* (group A beta-hemolytic streptococci).

Contraindications: Known allergy to cephalosporins.

Warnings: CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:

- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- In renal impairment, safe dosage of Ceclor may be lower than that usually recommended. Ceclor should be administered with caution in such patients.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include:

- Gastrointestinal (mostly diarrhea): 2.5%.
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, erythema multiforme, serum-sickness-like reactions): 1.5%; usually subside within a few days after cessation of therapy. These reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.
- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1%.

Abnormalities in laboratory results of uncertain etiology

- Slight elevations in hepatic enzymes.
- Transient fluctuations in leukocyte count (especially in infants and children)
- Abnormal urinalysis; elevations in BUN or serum creatinine
- Positive direct Coombs' test
- False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (glucose enzymatic test strip, Lilly)

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Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285.

Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630

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(Continued from Page 916)

PHYSICIANS WANTED

BEAUTIFUL SOUTHWEST WASHINGTON

The Camas Clinic And The Battle Ground Clinic, single practitioner offices, are seeking additional BC/BE Family Physicians. Both are affiliated with a large multispecialty clinic in Vancouver, Washington, and are located in rapidly growing small towns only 10-20 minutes away from community hospitals. These opportunities include two year Associate Agreements with full benefits and an opportunity for partnership after two years. Enjoy rural or suburban living with year round outdoor activities *and* the cultural benefits of nearby Portland, Oregon.

Contact:

Roger Garretson, Administrator
The Vancouver Clinic
700 N.E. 87th Ave
Vancouver, WA 98664
(206) 254-1240

ASSISTANT PROGRAM DIRECTOR or Faculty Person for Family Practice Clinic. Must have AAFP Boards. Would like to have private practice experience, but will evaluate applicant's overall strengths and will waive practice requirement in selected candidates. Strong program. Excellent opportunities in research, curriculum development, and teaching of clinical skills. Call or send CV to Bruce Nichols, MD, Director of Family Practice, San Joaquin General Hospital, (209) 946-6834, PO Box 1020, Stockton, CA 95201. AA/EOE.

SAN FRANCISCO BAY AREA—General Internist. Energetic BC/BE general internist needed immediately for 4 MD Fremont Satellite of Palo Alto Medical Clinic. Broad inpatient/outpatient IM practice in growing Bay Area community. Excellent location for family with convenient access to San Francisco. Please send CV to: Paul DeChant, MD, Fremont Center, 39500 Liberty St., Fremont, CA 94538.

OLYMPIA, WASHINGTON—Family Practitioner interested in associate. Attractive suburban setting. Salary guarantee with goal of eventual partnership. Excellent medical community in "America's Fourth Most Livable City." Send CV to Number 161, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ORTHOPAEDICS—Private practice opportunity in Espanola, New Mexico. Financial assistance with income guarantee. Easy access to all forms of recreation—only 20 miles north of Santa Fe. For further information, please submit CV to: Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or, call 1 (800) 545-4030, Ext. 8300.

OTOLARYNGOLOGIST: BC/BE and also interested in facial plastics to join 20 physician primary care and multispecialty group practice in beautiful Pacific Northwest setting. Reply to Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

OB/GYN: Multispecialty group in Northwest Washington desires second obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, Administration, 1400 E. Kincaid, Mount Vernon, WA 98273, (206) 428-2524.

BOARDED FAMILY PHYSICIAN to associate with established FP, obstetrics preferable, small practice gives opportunity for individualized care. Escondido Family Practice, 705 E. Ohio Ave., Escondido, CA 92025.

TWO PERSON INTERNAL MEDICINE practice in Sacramento suburb seeks Board certified Internist with/out subspecialty to join. Please send letter with CV to: American River Hospital, Alternative Delivery Systems, 4747 Engle Rd., Carmichael, CA 95608.

PHYSICIANS WANTED

SOUTHERN CALIFORNIA

Well-established and successful HMO is seeking Specialists and Primary Care physicians for our facilities in Los Angeles and Orange Counties. Located in close proximity to major teaching centers, we offer the opportunity for continued professional development and rewarding clinical practice. Excellent compensation and benefits package, including profit sharing. Please send CV to:

Director/Physician Recruitment
CIGNA Healthplans of California
700 N. Brand Blvd., Suite 500-49
Glendale, CA 91203

EMERGENCY PHYSICIAN needed to join new, expanding group in the beautiful Bitterroot Valley of western Montana. Contact J. G. Hansen, MD, PO Box 1262, Hamilton, MT 59840 or call (406) 363-2526.

TWO PHYSICIANS NEEDED to staff acute care/industrial medicine department with 70 physician multispecialty group near Sacramento. Experience preferred. Hours 8-8, weekdays only (40 hour week with flexible schedule). Clinic near 100 bed hospital. Full diagnostic services available in clinic and hospital. One position available immediately and one in spring, 1987. Contact: Michael Pirruccello, MD, Woodland Clinic Medical Group, 1207 Fairchild Ct., Woodland, CA 95695; (916) 666-2466.

IDAHO NEEDS FULL TIME EMERGENCY PHYSICIANS. 20 miles from Boise, near mountains and unlimited recreation. Excellent opportunity to affiliate with 162 bed hospital. ACLS—Yes. Contact M. Kutsurelis, Sr. Vice President, Mercy Medical Center, 1512 12th Avenue Rd., Nampa, ID 83651; phone (208) 467-1171.

TUCSON ARIZONA: Urgent Care, Family Practice, Internal Medicine, Pediatrics, OB/GYN. CIGNA Healthplan has career opportunities in Tucson, Arizona. Join a distinguished staff of experienced physicians; practice medicine without the administrative demands of private practice. Professional liability coverage, pension and retirement benefits, scheduled working hours, paid vacations, and CME benefits are provided along with a competitive salary. Please submit CV to: Director of Physician Recruitment, CIGNA Healthplan of Arizona, Inc., 4907 E. Broadway, Ste. 100, Tucson, AZ 85711; (602) 571-6517. Equal Opportunity Employer M/F/H/V.

SAN FRANCISCO BAY AREA. Directorship and full-time staff position available in a unique 24-hour free-standing medical facility. Affiliated with prestigious hospital in desirable San Ramon Valley of east San Francisco Bay Area. Postgraduate training in a primary care specialty and emergency department experience required. Partnership structure, growth potential, malpractice paid and benefits package available. Contact California Emergency Physicians, 440 Grand Ave., Ste. 500, Oakland, CA 94610; (415) 832-6400.

SAN DIEGO

Busy, multispecialty group in San Diego is expanding and will be adding Specialists and Family Physicians to its staff. Outstanding practice opportunities in an ideal geographic setting. For immediate consideration, please send CV to: Miriam Stephens, Director of Professional Recruitment, SMITH HANNA Medical Group, 5703 Oberlin Dr., Ste. 302-49, San Diego, CA 92121.

B/C-B/E DIAGNOSTIC RADIOLOGIST

Hospital and office practice. All modalities except MRI. Hands on experience in real time ultrasound desired. Excellent salary and benefits, commensurate with experience. Early partnership. Will consider locums. Send CV to Radiology, 5681 N. Fresno St., Fresno, CA 93710; (209)439-2464.

PHYSICIANS WANTED

ANESTHESIOLOGIST sought for the Espanola Hospital in Espanola, New Mexico. Financial assistance/income guarantee. For further information please submit CV to: Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or, call 1 (800) 545-4030, Ext. 8300.

BC/BE FAMILY PRACTITIONER is needed immediately to join, with the option of buying out, a very busy 30-year established private practice in Southeast New Mexico with a population of 14,000. Great place to raise a family—peaceful community with year-round recreation. Excellent weather; excellent school system. Fully-equipped, new 38 bed hospital. Financial package negotiable. Forward CV to: Professional Medical Office Building, Ste. D, 612 N. 13th St., Artesia, NM 88210.

ORTHOPEDIC SURGEON. California—Valley Medical Center of Fresno, a teaching hospital affiliated with the University of California, San Francisco, seeks an academically oriented orthopedic surgeon. The orthopedic service at Valley Medical Center supports a busy trauma service and participates actively in teaching of residents in general surgery, emergency medicine, and family medicine. Position requires experience in trauma. Pediatric experience is desirable. This position also offers private practice opportunities in a multispecialty group setting. The central California location offers ready access to both mountain and coastal areas. Please address inquiries and CVs to: Sergio Ilic, MD, Chief of Orthopedics, CCFMG, 2212 N. Winery, Fresno, CA 93703; (209) 252-1837. Equal Opportunity Employer.

INTAKE PHYSICIAN. For neurology practice. Conduct intake exams; administer diagnostic tests; prepare diagnoses; counsel patients. Req. MD plus completed 1 year internship in general medicine. Also at least 2 years experience in medical practice in internal medicine gastroenterology, or neurology. Req. license to practice medicine in Arizona (if without license duties will involve only interviewing, research and information sharing with patients until license completed). Must have experience in internal medicine, basic gastroenterology, and basic neurology. Also experience in patient histories, physicals, lab test orders and interp., nasogastric tube placement, endoscopy, rectosigmoidoscopy, rectal exams, abdominal, pleural, and lumbar taps, spinal fluid analysis, electroencephalograph testing, CT scan inter. Must have experience in patient counseling; fluent in English and Spanish. Salary: $60,000 per year. Qualif. applicants send résumé or application letter to: AZ DES Job Service Attn 732A re: 0802214, PO Box 6123, Phoenix, AZ 85005, no later than January 7, 1987. (Job Location: Tucson. Emp pd ad; proof of authorization to work in US required; list in résumé or app. letter.)

NORTHERN SAN FRANCISCO BAY AREA. Seeking physician Board certified or eligible in Internal Medicine for Internist position in growing department of medicine. Competitive salary and excellent benefits. Call or write: Chief, Department of Medicine, Kaiser Permanente Medical Center, 1550 Gateway Blvd., Fairfield, CA 94533; phone (707) 427-4200.

CARDIOLOGIST, INVASIVE/NONINVASIVE BC/BE to join busy cardiology department of multispecialty group in central California. Send CV to: David J. Cislowski, MD, FACC, 222 W. Willow St., Visalia, CA 93291.

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March 18—**New Directions in Gynecologic Research.** Seattle. Wednesday. U/W Health Sciences. Contact: U/W.

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April 17—**Basic Monitoring Laboratory.** Seattle. Friday. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

April 25—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 8—**Current Issues in Asbestos Control.** Seattle. Friday. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

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—Marsden S. Blois, PhD, MD

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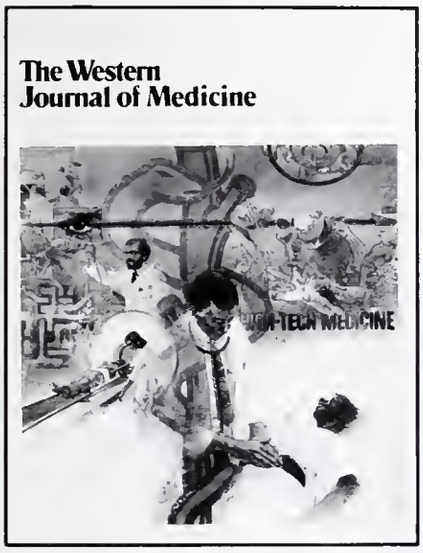

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—R. Paul Robertson, MD

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Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1987: Date and place to be announced.

Hawaii Medical Association—320 Ward Ave, Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: 1987: Date and place to be announced.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 27-August 2, 1987, Coeur d'Alene.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Interim Meeting: April 3-4, 1987, Colonial Inn, Helena.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 30-May 3, 1987, Ormsby House, Carson City.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 6-8, 1987, Clarion Four Seasons, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): April 3-4, 1987, Salishan Lodge, Lincoln City.

Utah State Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1987: Date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: 1987: Date and place to be announced.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 25-29, 1987, Jackson Lake Lodge, Moran.

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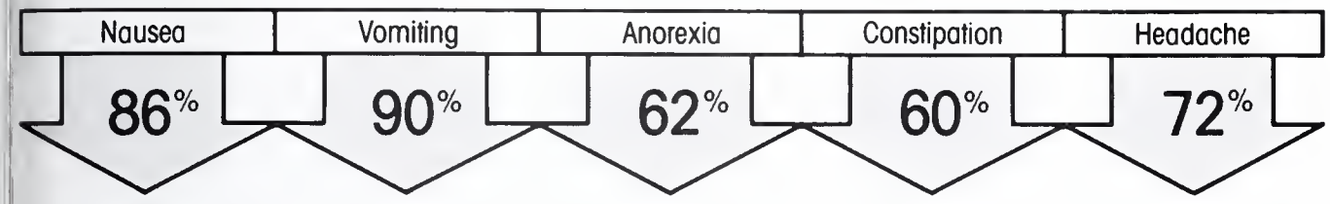

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References: 1. Data on file, Hoffmann-La Roche Inc., Nutley, NJ **2.** Feighner JP, *et al Psychopharmacology 61*:217-225, Mar 22, 1979

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Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage, withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady state concentrations of the tricyclic drugs. Concomitant use of Limbitrol with other psychotropic drugs has not been evaluated, sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol DS (double strength) Tablets, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol Tablets, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: *Double strength (DS) Tablets*, white, film-coated, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt), and *Tablets*, blue, film-coated, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt). Available in bottles of 100 and 500, Tel-E-Dose® packages of 100, Prescription Paks of 50.

ROCHE®

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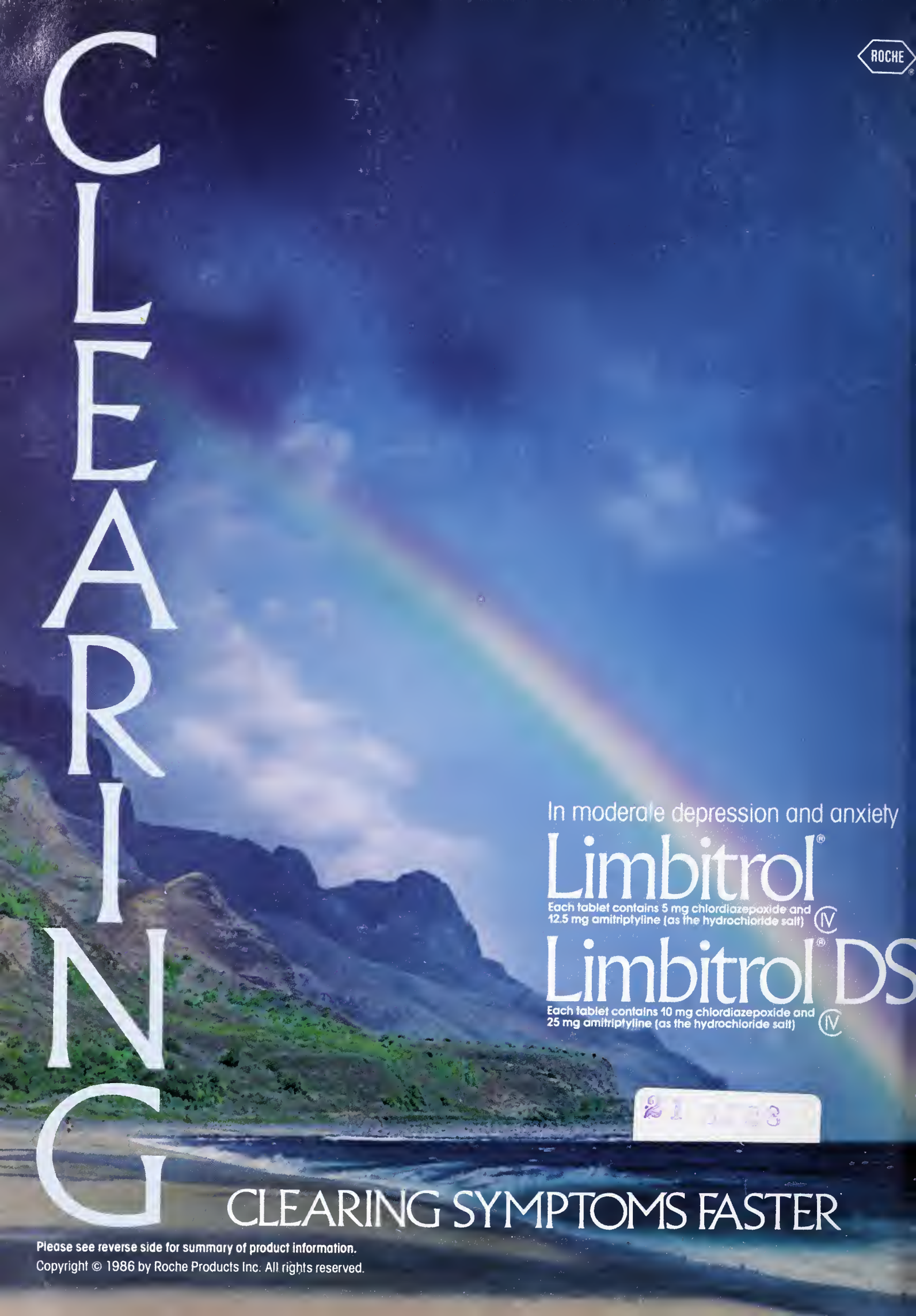

Please see reverse side for summary of product information.

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